OXIDATION-REDUCTION REACTIONS OF MORPHINE IN DIFFERENT MEDIA

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CHAPTER I

INTRODUCTION

Morphine, the naturally occurring alkaloid or nitrogenous base, is found principally in opium, which is the dried sap of the unripe seed capsule of Papaver somniferum and is present to about 10% by weight of the total alkaloid extract. Other important alkaloids are codeine, thebaine and papaverine which together make up 30% by weight (1). Morphine was isolated from opium being the first "vegetable base" reported by Serturner in 1805 (2). Methods of isolation, structural determination, synthesis and physical properties of morphine have been summarized by Bentley and Holmes (3, 4).

Morphine is very readily oxidized, reducing gold and silver salts to the metals (5). Mild oxidation of morphine by a variety of reagents, especially in alkaline solutions, and including atmospheric oxygen in ammonia (6) condenses together two molecules of morphine to produce a dimer referred to most commonly as pseudomorphine. The molecule is also less frequently referred to as oxymorphine. oxydimorphine, dehydromorphine and pormine (7).

Pseudomorphine was first described in 1835 by Pelletier (8) in an investigation of the alkaloids

obtained from opium, and its characteristic properties were studied. It was noted that pseudomorphine is physiologically inert and undergoes further oxidation easily. In opium it is present to only 0.02% by weight (9) and is most likely produced from the partial oxidation of morphine. No evidence for further oxidation in the plant is available. There is no adequate proof that pseudomorphine is a metabolite of morphine in human organisms (7). The chemistry and the structure are not well known. It has been studied only in a desultory way and over a long period of years. However, it was reported as a first oxidation product of morphine (10). It was proposed by Bentley and Dyke (11) that the structure of the product was a 2,2'-dimer. Small and Turnbull (12) on the other hand suggested that it was a 1,1'-dimer. This ambiguity has not been resolved. Only two physical methods were applied to the identification of pseudomorphine, namely UV and fluorescence spectroscopy (11, 13).

Morphine is classified as a controlled or illegal substance. Its abuse is of international concern. Rapid identification is critical in pharmaceutical, clinical and forensic science applications. The formation of pseudomorphine has been suggested as a confirmatory test for the identification of morphine (14). Besides the formation of pseudomorphine, there are several other physical and chemical methods employed in the identification and/or determination of morphine e.g. UV-visible (15), IR (16),

and NMR spectroscopy (17, 18, 19), chromatography (20, 21, 22), circular dichroism (23), microcrystalline tests (24) and color spot tests (25). Color spot tests are the area of interest to this study.

Color Tests are used as a preliminary screen to place an anonymous substance into a particular classification group which expedites its identification. None of the tests is specific for any drug in that members of the same group will react similarly with the test reagent to produce a consistent color. The color test method was introduced by Dragendorff (26) in 1868 and was developed for the identification of drugs by Umberger (27). Most of the color test reagents used for opium alkaloids require concentrated sulfuric acid as the reaction solvent and some oxidative metal salts. It was reported by Fulton in 1928 (28) that morphine develops a series of colors in the sulfuric acid solution itself. In the same paper, he also postulated that the product was not apomorphine as most authorities had intimated (p. 24):

> The statements in the textbooks as to the compound formed on heating morphine in sulfuric acid seem to be nothing more than poor guesses.

These very empirical color tests have been used although little is known about the chemistry involved including the mechanisms and the identities of the products formed. Possible interfering reactions have been identified; however, in 1964, Schieser (29) described an ESR study of a number of color test solutions for alkaloids,

and specifically for morphine sulfate. His results suggested that the reactions involved free radicals and the changes in color with time were due to the formation of different free-radical anions which appeared concurrently with each color. He also suggested that the site of radical formation in the alkaloid is the aromatic ring moiety. No reaction mechanism was proposed. In 1975, Ahlers and Auterhoff (30) used UV-visible, IR spectroscopy and thin-layer chromatography to identify the products of the morphine after reaction with the color test reagents developed by Froehde, Mandelin and Erdmann. They concluded that the product is an o-quinone of apomorphine. Again the chemistry and the complex mechanisms of these reactions are as yet unexplained.

The metals in the inorganically based color reagents are for the most part in their highest oxidation state, so reduction of these complex salts by the alkaloid is implied. Accordingly, this study covers the oxidation of morphine under two different conditions: the mild conditions pertaining to the alkaline medium and the more severe conditions which prevail in concentrated sulfuric acid. A variety of experimental and instrumental techniques have been applied to the study of these processes with a view to revealing additional information on the products so that the complexities of the reactions might be better interpreted.

Statement of the Problem

This research was undertaken to study the redox reactions of morphine in basic, neutral and strong acid solutions. The chemistry and mechanisms of the reactions and the structures of the products in these reactions are of interest.

The particular physical methods used in the study are circular dichroism (CD), nuclear magnetic resonance (NMR) and X-ray crystallography. The background and theory of these techniques are discussed in the following chapter. Details of the reactions and structural information on the products are presented in subsequent chapters.

CHAPTER II

BACKGROUND AND THEORY

Circular Dichroism

Circular dichroism (CD) is a useful spectroscopic technique when applied to structural determinations of compounds having one or more optically active sites. Besides being optically active the compounds which are CD active must also contain a chromophore to absorb electromagnetic radiation. As such CD is simply a modification of absorption spectrophotometry. The basic difference is that the incident light is circularly polarized and the experimental parameter measured is the difference in absorption of the left and right circular components. It is most amenable to studies of molecules in solution, but has been applied to a few solids supported in KBr pellets.

To understand the basic theory of CD, one should begin with the discussion of the properties of light. Ordinary light behaves as if it consisted of a large number of electromagnetic waves oscillating in all possible orientations around the direction of propagation. The electric and magnetic fields associated with the propagating

beam oscillate at right angles to each other and perpendicular to the beam direction. By passing the beam through special devices known as polarizer elements, only waves oscillating in a particular plane are transmitted. Devices are available for the infrared, visible and ultraviolet ranges of the electromagnetic spectrum. The transmitted beam is commonly referred to as plane-polarized light. Considering only the electric vector E of the plane-polarized beam, it cah be represented as consisting of two circularly polarized components moving in vacuo at the same speed. The vectors are imagined to rotate in opposite directions at the same angular velocity determined by the refractive index (n) of the medium. Their vectors can be represented by E_L (left rotation) and E_R (right rotation) as shown in Figure 1. So long as the angular velocities are equal the vector sum is E oscillating in the direction of the original plane of polarization. If the angular velocities differ, $\omega \neq \omega'$, then the vector sum is no longer directed along the original plane but is rotated out of that plane by an angle α.

For Figure 2 $\omega > \omega'$ and rotation is to the right. The only reason angular velocities would differ is that the medium through which the beam passes would have a different refractive index for each polarization, i.e. $n_L \neq n_R$. When this occurs the medium is said to be circular birefringent. E lies in the direction of the

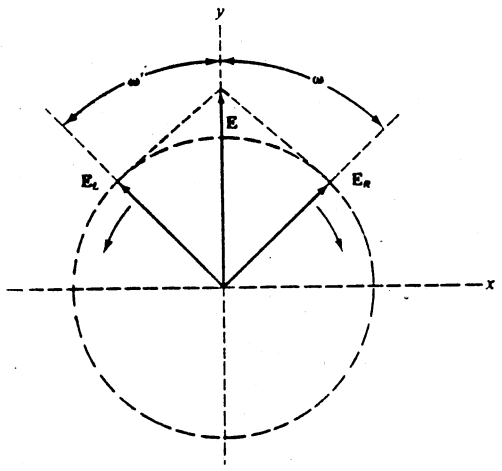


Figure 1. End View of Electric Field Vector E as the Resultant of Two Rotating Vectors, E_L and E_R

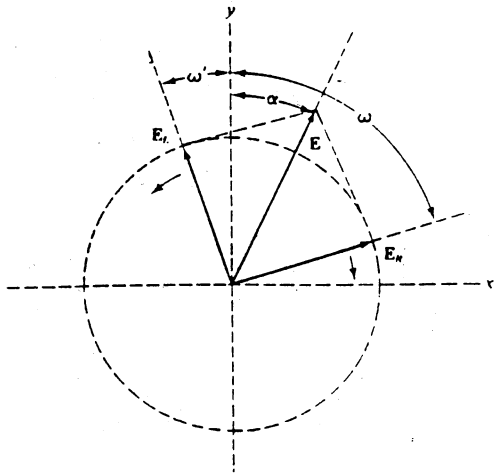


Figure 2. End View of Electric Vectors on Passage of Plane-Polarized Light Through an Optically Active Material

diagonal line of the square whose sides are E_L and E_R.

Since n_L and n_R are wavelength dependent, α varies as a function of wavelength. The spectrum of α plotted versus the wavelength λ is called Optical Rotatory Dispersion (ORD). The relationship was described mathematically by Fresnel (32) according to equation (2.1).

$$\alpha = \pi/\lambda(n_L - n_R) \qquad (2.1)$$

where: α has units of radians per unit length and λ is the incident light wavelength.

Media which are circularly birefringent are optically active. For solutions the activity is a consequence of dissolved chiral molecules. The property α is, as expected, dependent upon the solution concentration. To normalize α for comparison among solutions of different concentrations, a quantity known as the specific rotation $[\alpha]$ is defined, equation (2.2).

$$[\alpha] = 1800 * \alpha/c * \pi \qquad (2.2)$$

where: c is the concentration in grams per milliliter of a solution, and $1800/\pi$ is the conversion factor needed to give the specific rotation in degrees per decimeter.

To allow for comparisons among different compounds in solutions of different concentrations, the more general molecular rotation $[\Phi]$ term is defined, equation (2.3).

$$[\Phi] = [\alpha] * M/100 \qquad (2.3)$$

where: M is the molecular weight of the optically active substance.

If the optically active medium contains a compound which absorbs energy from the beam then not only the speed of rotation will change but also the compound will absorb left and right circularly polarized light to different extents. Therefore in the spectral regions where optically active absorption bands are present, the length of vector E_R is no longer equal to E_L, and their resultant E no longer oscillates along the circumference of a circle. Instead, the resultant vector E now traces out an ellipse, as shown in Figure 3.

The emitted light is said to be elliptically polarized and the medium is said to exhibit circular dichroism. In terms of quantum mechanics, this means that the transition probabilities are different for left and right circularly polarized light (33). The resulting ellipse is characterized by the angle of ellipticity, θ, which is given by the following equation (2.4).

$$\theta = \pi * (A_L - A_R)/\lambda \qquad (2.4)$$

where: A_L and A_R are the absorbances for the left and right circularly polarized components, respectively. The A values are related to the molar absorbances, ε, and the molar concentration C of the absorbing substance by equation (2.5).

$$A = \varepsilon * b * d \qquad (2.5)$$

By analogy with specific rotation, the specific ellipticity $[\theta]$ is defined by equation (2.6).

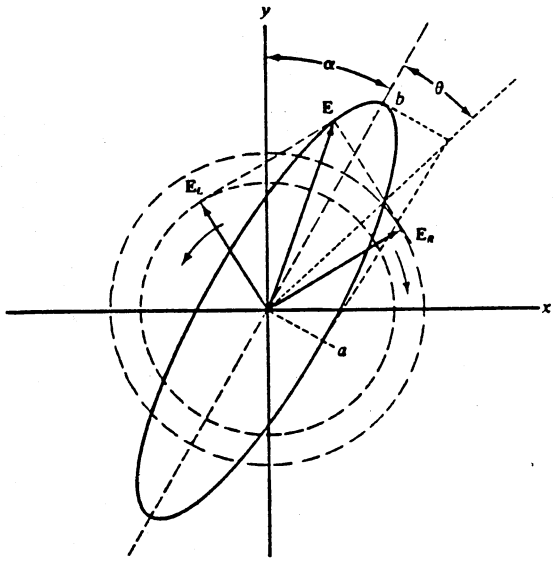


Figure 3. End View of Electric Field Vectors on Passage of Plane-polarized Light Through an Optically Active Material. The wavelength of light is within an absorption band.

$$[\theta] = \theta/lc \qquad (2.6)$$

where: θ is measured in degrees, l is the path length in decimeters and c is the concentration in grams per milliliter of solution.

Similarly, the molar ellipticity $[\Psi]$ is defined by equation (2.7).

$$[\Psi] = [\theta]M/100 = \theta/Cd = 3000\ (\varepsilon_L - \varepsilon_R) \qquad (2.7)$$

where: d is the path length in centimeters and C is the molar concentration of absorbing species.

CD spectra are obtained by measuring the ellipticity θ as a function of wavelength λ. The spectra may show positive and/or negative peak(s). The wavelengths of the maxima are referred to as λ^{+}_{max} or λ^{-}_{max}. These maxima and the wavelength(s) of crossover point(s) (λ^{o}) are characteristics of each CD active compound and can be used for qualitative distinction. All CD curves, by definition, are Cotton effect curves which are named in honor of the French physicist, Aime Cotton, who discovered this phenomenon in 1896 (34).

Since CD is a modified form of absorption spectroscopy, the method is not only useful in compound identification but also in quantitative analysis, kinetic studies, and stereochemical conformational assignments.

Nuclear Magnetic Resonance

Nuclear Magnetic Resonance spectroscopy (NMR) is a

branch of chemical spectroscopy which concerns radio-frequency (rf) induced transition between quantized energy states of magnetic nuclei that have been oriented by magnetic fields.

A fundamental property of an atomic nucleus besides mass and charge is the nuclear spin quantum number or nuclear spin (I) which has values 0, 1/2, 1, 3/2, ... etc. in units of h/2, where h is Planck's constant. The actual value of the nuclear spin of any given nucleus depends on the mass number and atomic number. The empirical rules relating the mass number and atomic number to nuclear spin are:

1. If both the mass number and the atomic number are even then I = 0.
2. If the mass number is odd and the atomic number is odd or even then I has half-integral values.
3. If the mass number is even and the atomic number is odd then I has integral values.

Both protons and neutrons have nuclear spin = 1/2, an unpaired nuclear spin leads to a nuclear moment (μ) given by the equation (2.8).

$$\mu = \gamma Ih/2\pi \qquad (2.8)$$

where: γ is the magnetogyric ratio which is constant for each particular nucleus.

In general, there are 2I + 1 possible orientations or states of the nucleus derived from the value of the magnetic quantum number (m_x).

$$m_x = I, (I-1), \ldots, -I$$

The most commonly encountered nucleus in NMR (^1H and ^{13}C) has a value of I equal to 1/2, therefore $m_x = \pm 1/2$. These states have the same energy in the absence of a magnetic field. When a uniform magnetic field of strength H_o is applied, the states are no longer degenerate as shown in Figure 4.

Nuclei for which $I \neq 0$ behave as minute bar magnets whose axes coincide with the axis of spin. When these nuclei are made to spin in a powerful uniform magnetic field (H_o), they do not flip over to align their magnetic moments with the field but instead align themselves at some angle θ with respect to the direction of the field and their spin axes undergo precessions about the H_o axis as shown in Figure 5. The precission frequency (ω_o) is measured in radians per second. The angular velocity ω_o is independent of θ but is proportional to the field strength H_o as shown in equation (2.9).

$$\omega_o = \gamma H_o \tag{2.9}$$

When a second small magnetic field H_1 (represented by the horizontal vector in Figure 6) is applied at an angle perpendicular to H_o and is rotated about the H_o axis with an angular frequency ν_o, then the spinning nuclei will absorb energy and flip into a higher energy level, if ν_o is exactly equal to the precession frequency ω_o. The rotating nuclear magnetic moment is in resonance with the

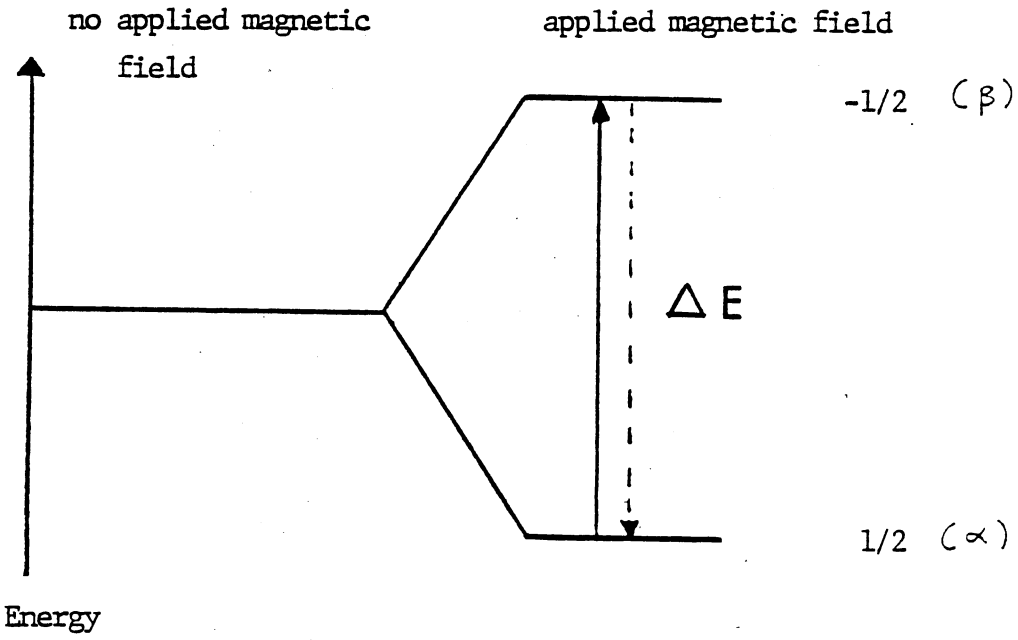


Figure 4. Energy Levels and Transitions for a Nucleus (I=1/2) in a Magnetic Field

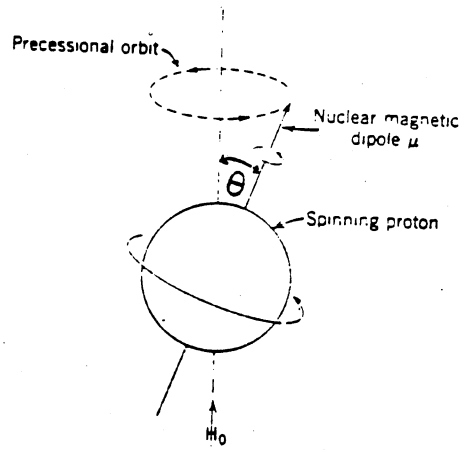


Figure 5. Proton Processing in a Magnetic Field (H_o)

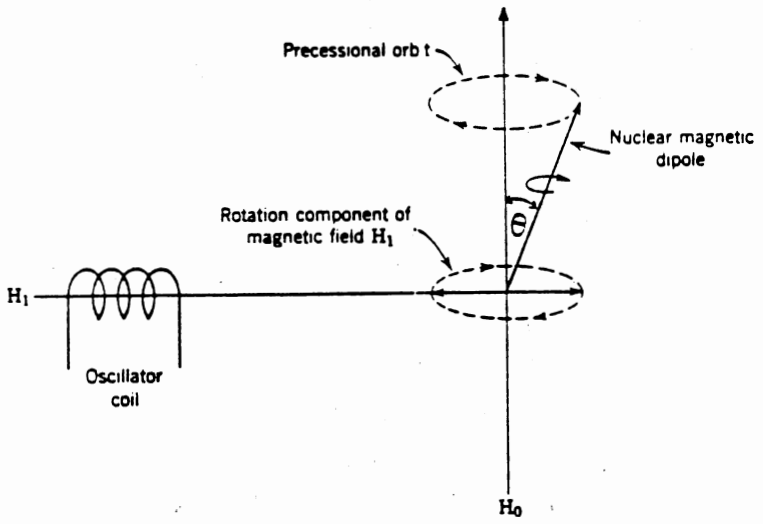


Figure 6. Oscillator Generates Rotating Component of Magentic Field H_1

field H_1 and the absorption energy (ΔE) is given by

$$\Delta E = h\nu_o = \mu H_o / I \qquad (2.10)$$

The selection rules for NMR which establish the resonance conditions are:

1. $\Delta m_x = \pm 1$
2. $\Delta E = \gamma h H_o / 2\pi$
3. $\nu_o = \gamma H_o / 2\pi = \omega_o / 2\pi$

Let us consider a nucleus of spin 1/2 which has two possible orientations of nuclear spin α and β. The coefficients for the absorption and emission of energy between these states are equal for NMR and therefore there would be no net energy transfer from the radiation source to the sample if the population of the two states were equal. However, the sample is in thermal equilibrium and the Boltzmann distribution of energies is maintained.

$$N_\beta / N_\alpha = \exp(-h\nu_o / kT) \qquad (2.11)$$

If $h\nu_o << kT$, then

$$N_\beta / N_\alpha = 1 - h\nu_o / kT \qquad (2.12)$$

Whenever $N_\beta < N_\alpha$ a net absorption occurs. In the rf spectral region (5-400 MHz), values of $h\nu_o$ are on the order of 1E-2 cal. Therefore the excess population of spins in the lower state is 1E-5 for ambient temperatures. For this reason NMR is less sensitive than either IR or UV spectroscopy. However the coefficient of absorption is a constant for any given nucleus. Therefore the observed

NMR signal intensity is directly proportional to the number of nuclei producing it. Obviously, the populations of the spin states are perturbed on the absorption of radiation. The system relaxes to the original Boltzmann distribution by two mechanisms. These are spin-spin relaxation and spin-lattice relaxation.

In the spin-spin relaxation mechanism, a nucleus in its upper spin state transfers its energy to a neighboring nucleus of the same isotope by a mutual exchange of spins. This relaxation process does not change the relative spin state population and therefore does nothing to maintain the absorption condition, but it does shorten the lifetime of a given nucleus in the higher state and therefore produces line broadening.

In spin-lattice relaxation, energy from the nuclear spin at higher energy is converted into thermal energy. The high-energy spin state must be properly oriented with respect to the lattice molecules, such that energy can be transferred to the lattice molecules, giving them extra translational or rotational energy. This process is directly responsible for maintaining the unequal distribution of spin states. As a result there is always an excess of nuclei in the lower energy state, and a continuous absorption of energy from the rf source by the sample can occur.

Information Available from NMR Spectroscopy

Each nucleus in a molecule has a different electronic environment. The magnetic field associated with the electronic movement around a nucleus interacts with the applied magnetic field H_o, which successfully shields the applied magnetic field H^o. The extent to which H_o is reduced depends upon the shielding constant (6) which is different for different nuclei. The effective magnetic field at the nucleus (H_{eff}) is given by equation (2.13).

$$H_{eff} = H\ (1 - \sigma) \qquad (2.13)$$

σ is a characteristic property for each nucleus in a given electronic environment and has a nondimensional value from zero to one.

For the above reason, different resonance conditions prevail for different nuclei. Each resonance can be excited in turn either by varying the frequency ν_o at constant H_o or varying H_o at constant ν_o. Data are usually obtained in the form of a spectrum in which resonance intensities are plotted as a function of ν_o at constant H_o.

Since ν_o and H_o are mutually dependent parameters, ν_o is not a general characteristic quantity since it will vary with H_o for any given nucleus. To overcome this inconvenient problem, a chemical shift (δ) term is introduced. This term is defined to be independent of H_o and ν_o and depends only upon the molecular environment. Nuclei

which have identical environments will have the same chemical shift. The chemical shift is defined as

$$\delta = \Delta\nu * 1E6/\text{oscillator frequency} \quad (\text{ppm})$$

where, $\Delta\nu$ is the difference between the radio-frequency at which energy is absorbed by a reference nucleus and the resonance frequency for the nucleus of interest. By using a difference measurement made under identical experimental conditions it is not necessary to determine H_{off}, a term which is difficult to obtain with any accuracy. In practice the relative resonance frequencies between the sample and the reference are measured, and δ for each nucleus is obtained from its displacement on the frequency scale from the standard which is arbitrarily set at zero ppm. Since the oscillator frequency is in units of MHz but $\Delta\nu$ is in units of Hz, the fraction is multiplied by 1E6 to give numbers for δ which are more convenient to use.

Reference compounds must be unreactive and have resonance frequencies in a range which do not overlap or coincide with those for the compounds of interest. Common reference materials are tetramethylsilane (TMS) for non-aqueous solvents and sodium 2,2-dimethyl-2-silapentane-5-sulphonate (DSS) for aqueous solutions.

By convention, NMR spectra are reported in such a fashion that the field increases from left to right. In a comparison of nuclei, the more shielded nuclei are upfield (on the right of the spectra) and the less shielded nuclei are downfield (on the left of spectra).

Chemical shift data are used to distinguish among the types of nuclei. The area under each peak at a given chemical shift is used to determine the number of identical nuclei which contribute to that peak. Determination requires a peak integration step which is a standard electronic capability of all spectrometers. Integrations under ^{1}H peaks can be done with ± 2% accuracy. For ^{13}C however, integrations are less reliable because of the low natural abundance of the isotope.

In high resolution NMR such as Fourier transform (FT) NMR, spin-spin coupling data are the other useful experimental parameters. Spin-spin coupling is a consequence of interactions between nuclear spins of nuclei which are either adjacent or separated by several intervening bonds. A narrow splitting of energy levels allows for several transitions to occur, which produce groups of lines around the principal resonance band referred to as multiplets. The magnitude of the interaction between two nuclei in a particular environment is expressed in terms of a spin-spin coupling constant in Hz (J_{AB}) which is independent of the applied magnetic field. However the analysis of spin-spin multiplets is applicable only under first-order analysis conditions. These conditions are:

1. The magnitude of the chemical shift difference between the nuclei or the group of nuclei must be larger than the spin-spin coupling constant between them.

2. The coupling must involve groups of nuclei that

are magnetically equivalent, not just chemically equivalent.

When first-order analysis is applicable, then

1. A nucleus or a group of nuclei coupled to a set of n nuclei with spin I will have the principal resonance split to 2nI+1 lines.

2. The relative intensities of the 2nI+1 lines are given by the coefficients of the terms in the binomial expansion of $(x+1)^n$.

3. The 2nI+1 lines are separated by equivalent coupling constants.

4. The coupling between a magnetically equivalent set of nuclei does not affect the spectrum.

Since each nucleus in a molecule is capable of coupling with every other nucleus, a spectrum composed of many multiplet sets is generated. Some electronic techniques are introduced in order to simplify the spectrum such as double resonance or spin decoupling and off-resonance decoupling. The two techniques involve the application of a strong magnetic field oscillating at a frequency close to the resonance frequency of a given nucleus which isolates it from interactions with other nuclei in the molecule. If sufficient radiative power is applied, the "isolated" nucleus will flip reversibly between α and β states so rapidly that the states are indistinguishable to other nuclei and only an average orientation is observed. Coupling between this and other nuclei disappears and the signal collapses to give a

singlet line as seen in a ^{13}C NMR fully proton decoupled spectrum. In the other case, that of off-resonance decoupling, a lower decoupling power is selected such that only the long range ^{13}C-^{1}H coupling are diminished. Then only the first neighbor ^{13}C-^{1}H couplings are observed. From the resultant simplified spectrum, assignments for each carbon can be made. Primary, secondary, tertiary and quaternary carbons in the structure are easily distinguishable as quartets, triplets, doublets and singlets, respectively.

X-ray Diffraction

X-rays are rays of electromagnetic radiation of wavelength between .1-100 A^{o}. The most useful region for analytical purpose is 0.7 to 2.0 A^{o}. A single crystal X-ray diffraction method is based on the scattering of the X-rays by a single crystal of the compound being investigated. The scattering produces a diffraction pattern only when certain geometrical conditions as expressed by Bragg's law are satisfied. Diffraction patterns may be used to identify molecules and molecular structures.

To generate the X-rays, electrons from a hot cathode accelerated by a high voltage field (20-50 KV) attach to an anode target which is a plate made from a single element, of moderate atomic weight, in an evacuated chamber. When the beam of electrons impinges on the target, the electrons in general are decelerated by multiple interactions with

the electrons of the target. The energy lost is converted into a continuous or white radiation.

As the voltage is increased to a point where the energy is sufficient to knock an innermost (K shell) electron out of the target atom, then an electron from an outer shell falls back into the vacancy. A photon of X-ray is emitted with a wavelength determined by the energy difference between the levels, and hence is characteristic of the target element. When the vacancy is filled by an electron from the L shell or M shell, then the emitted X-radiations are designated as K_{α} and K_{β} radiations, respectively as shown in Figure 7.

For the single crystal X-ray diffraction, a strong monochromatic beam is needed. This can be obtained by:

1. Choosing characteristic emission lines which are much stronger than the others, and isolating these with the aid of a filter.

2. Using a single crystal aligned at a particular angle and in a specific plane which acts as a monochromatic source. According to Bragg's law (36), the crystal will produce a specific wavelength of reflection.

When the beam of X-rays is passed into the single crystal, which is represented by layers of particles as shown in Figure 8, the X-rays are scattered by interaction with electrons in the atoms or ions of the crystal. The scattered waves would interfere constructively when the conditions for reflection of the beam satisfy the Bragg's

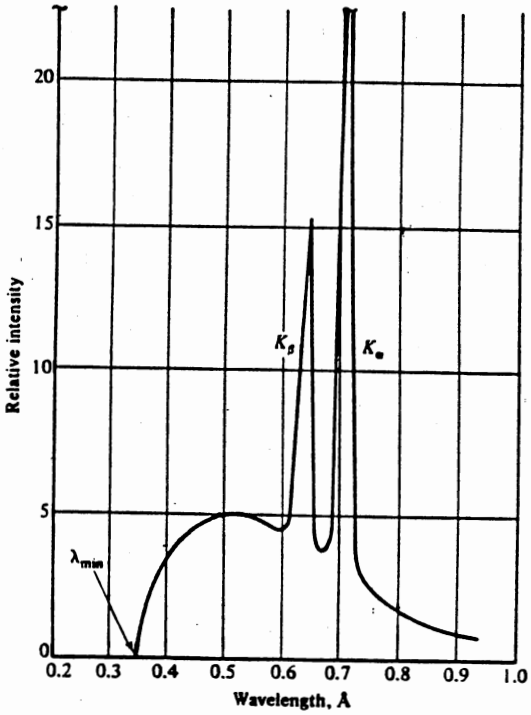


Figure 7. X-ray Spectra with Characteristic Peaks from a Molybdenum Anode X-ray Tube Operated at 35 kV

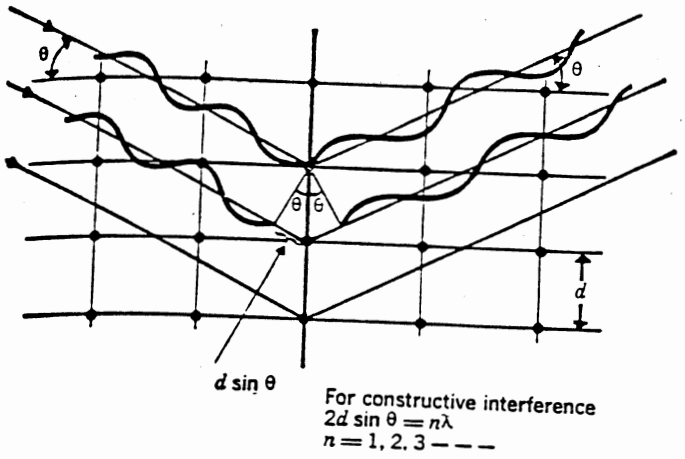


Figure 8. The Bragg Scattering Condition

law according to the following equation,

$$n\lambda = 2d \sin \theta$$

when n is an order of reflection. In single crystal X-ray diffraction, n is equal to 1. λ is the wavelength of the emitted x-radiation which strikes between parallel planes separated by a distance d, and at an angle θ equal to the angle of reflection.

The intensities of the beams depend upon the type and the location of the atoms in the fundamental repetitive units of the crystal.

In practice the crystal is rotated around preselected axes such that various sets of planes assume the orientations for Bragg reflections. These planes are defined by three integers h, k and l referred to as the Miller indices. In inverse space h, k and l are defined by a/x', b/y' and c/z', where a, b and c are the unit cell dimensions and x', y' and z' are the fractions of a, b and c cut by the plane, respectively. The intensities of the reflections from each plane are detected by a counter and electronically recorded by a dedicated computer.

From the relationship between the reflection intensities at each Miller index plane and Bragg law, the cell dimension (a, b, c) and the angles of the unit cell (α, β, γ) are computed. Using this information, a crystal system can be identified. Each crystal system may belong to several different space groups, with different symmetries, depending upon the number of molecules in one unit cell

(Z). Z can be calculated knowing the molecular weight and the density (D) of the molecule from the relationship

$$D = 1.6602 * M.W. * Z/V$$

v is a volume of the unit cell. D is usually in the range 1.1-1.5 g/cc for most organic compounds and 1.6-2.1 g/cc for most organometallic compounds.

Space groups and the equivalent general position of any particular space group generated from symmetry elements which correspond to that space group are listed in the "International Table for X-ray Crystallography" (37). Intensity data are reduced to obtain structural factors from which an electron density map can be calculated thereby locating the atomic positions in the molecule. Bond lengths and bond angles between atoms in the molecule are subsequently determined.

It is clear from the preceding remarks that X-ray crystallography is an unambiguous technique which provides a complete three dimensional picture of a molecule in the solid state. Structural information is frequently extrapolated from the solid to the solution state to complement information from other methods which are applicable to solutions, e.g. NMR and CD. These three methods have been used in this study of morphine derivatives and products from reactions of morphine with oxidizing agents.

CHAPTER III

EXPERIMENTAL

Instruments

Circular dichroism measurements were made on a JASCO (Japan Spectroscopic Company) model J-500A automatic recording spectropolarimeter. Data collection and manipulation was done either manually or with the data processor Model DP-500N accessory.

The instrument has a wavelength range from 180 to 800 nanometer (nm) and a sensitivity scale from .1 to 50 millidegree per centimeter (m^{o}/cm).

The light source is a 450 watt high pressure Xe arc lamp cooled by the flow of water at approximately 2L/min. The instrument is operated under 23 amp lamp current, and 105 volt line voltage. It is continuously purged with nigrogen gas boiled from a liquid nitrogen dewar at a flow rate of about 2L/min in order to prevent the production and accumulation of ozone from oxygen by UV radiation which would cause deterioration of the optics system.

The ellipticity scale is calibrated using a 0.05% (W/V) androsterone/dioxane solution in a 10 mm cell. The wavelength is scanned from 350 to 250 nm and the CD peak

height at 304 nm maximum is set equal to 96.2 mm of chart scale at sensitivity 20 m^{o}/cm. Baseline corrections were made for the solvent blank by spectral subtraction on the data processor. Sensitivity, scan rate, time constant and repeat time functions were selected which optimized the S/N ratio. The cells used for the analyses were made from quartz crystal. Path lengths of 1 or 10 millimeters were used, determined by the concentration of the solution under study.

UV-visible spectral measurements were made on a Perkin-Elmer UV-visible spectrophotometer Model 552, which is a double beam instrument. The light sources are tungsten-bromide and deuterium lamps with an automatic change made at 315 nm. This instrument has a wavelength range from 190 to 900 nm with ± 0.5 nm accuracy. The instrument is equipped with an automatic baseline adjustment and is connected to the Perkin-Elmer recorder Model 561 which has an accuracy less than ± 0.4% of span. The accessible absorbance range is from 0.000 to 3.000 absorbance unit (A). Measurements were made using a scan speed of 120 nm/min, a recording speed of 20 nm/cm and slit width 1 nm.

NMR spectra were run on a Varian XL-300 multinuclear NMR spectrometer with the fixed magnetic field strength 7.05 Telsa (1 Telsa = 1E4 Gauss) and the resonance frequencies of ^{1}H and ^{13}C nuclei at 299.944 and 75.45 MHz, respectively. Sample tubes of 5 mm o.d. were used for all

measurements. Chemical shifts were recorded from 0 to 10 ppm for ^{1}H and from 0 to 200 ppm for ^{13}C spectra, respectively.

X-ray structural determinations of the morphine derivatives and its oxidation product were done on a four-circle automated diffractometer Model Syntex P3. The instrument uses molybdenum radiation (λ = 0.71069 A^{o}) with a graphite monochromator fixed at an angle of 6.1^{o} with respect to the beam as it emerges from the X-ray tube and impinges on the 110 plane.

Mass spectra were made on a CEC 21-110B high resolution spectrometer. It is equipped with a Data General NOVA 3112 DS-50S data system.

Weighings were made on two balances. A Sartorius balance (Model 2403) was used for sample weights in excess of 10 mg. A Cahn electrobalance (Model 2000RG) was used for the sample sizes in the 0.001 mg to 10.000 mg range.

Chemicals

Morphine sulfate pentahydrate and morphine free base were the main starting reagents used in this study. Both were pure standard reagents, which were obtained from Mallinckrodt Inc., and from the National Institute for Drug Abuse (NIDA) via the Research Triangle Laboratories (RTI), respectively. Apomorphine hydrochloride was obtained from Applied Science Division and used without further purification. Distilled water and deionized water

were used as solvents for neutral and basic reactions while concentrated sulfuric acid, 98.0%, obtained from Fisher Scientific Company was used as the solvent in the acid reactions. Other reagents used in acid, neutral and basic reactions of morphine and its derivatives are listed in Tables I and II.

TABLE I

REAGENTS USED IN ACID OXIDATION REACTION OF MORPHINE

Reagent	Supplier
Ammonium molybdate $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$	Mallinckrodt
Ammonium vanadate NH_4VO_3	Fisher Scientific Company
Selenious acid (98%) H_2SeO_3	Aldrich Chemical Company, Inc.
Chloroform (spectra-analyzed grade) $CHCl_3$	Fisher Scientific Company

Methyl iodide and methanol were obtained from Fisher Scientific Company. Phenol, o,o'-biphenol (99%), anisole, 3,3'-bianisole (97%) and the NMR deuterated solvent, DMSO(d6) were obtained from Aldrich Chemical Company, Inc.

TLC-plates used in the separation of the mixtures were obtained from Analtech. All reagents are reagent grade unless specified and they were used without any further purification.

TABLE II

REAGENTS USED IN NEUTRAL AND BASIC REACTIONS OF MORPHINE

Reagent	Supplier
Cadmium chloride	J. T. Baker Chemical Company
Copper sulfate pentahydrage	Fisher Scientific Company
Lead Chloride	J. T. Baker Chemical Company
Nickelous chloride	J. T. Baker Chemical Company
Potassium hydroxide	Mallinckrodt Inc.
Potassium ferricyanide	Fisher Scientific Company
Potassium permanganate	J. T. Baker Chemical Company
Silver nitrate	Fisher Scientific Company
Zinc chloride	Mallinckrodt Inc.

Experimental Procedures

Oxidation Reaction of Morphine in Basic Solution

Pseudomorphine was prepared by following the procedure reported by Bentley (11). The white water-insoluble product was recrystallized from a 1:1 mixture of concentrated ammonium hydroxide and distilled water. Fine crystals formed after two days. The recrystallized product was used for CD, UV and NMR studies. An attempt was made to grow single crystals of pseudomorphine and its derivatives such as dihydrochloride, dihydrobromide, monosulfate and monotartrate salts (38) for an X-ray structural study of pseudomorphine.

Oxidation Reaction of Morphine by Metal Ions in Aqueous Solution

The metal salts used in this study were silver nitrate ($AgNO_3$), cadmium chloride ($CdCl_2$), copper sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$), lead chloride ($PbCl_2$), nickelous chloride ($NiCl_2$), zinc chloride ($ZnCl_2$) and potassium ferricyanide ($K_3Fe(CN)_6$). The salts were dissolved in distilled water in which the mole ratio of the metal ion to morphine from base was equal to 10:1. For Ag^{+1} a systematic study was made in which the ratio was varied 1:1 to 10:1 in deionized water. The morphine free base concentrations used in these reactions were in the range

of 1.5E-4 to 3.5E-5 M.

Oxidation of Pseudomorphine. Potassium permanganate ($KMnO_4$) in .2% KOH and the various metal ions as mentioned above were also used for experiments in which pseudomorphine was oxidized.

Oxidation of Morphine and Apomorphine in Strong Acid Solution

The acid used in this study was concentrated H_2SO_4 which is a common solvent used in most of the color test reagents for screening opium alkaloids as shown in Table III. The color test reagents used were the Froehde, Mecke, and Mandelin reagents.

1. 200 mg portions of morphine sulfate were added to 50 ml concentrated H_2SO_4 and to similar solutions containing the three color test reagents. CD and UV-visible spectra of the solutions were recorded after appropriate dilution with the solvent. The solutions were allowed to stand at room temperature for a period of time (2 days for color test reagents and 16 days for only concentrated sulfuric acid) before being diluted with distilled water and extracted with chloroform. Chloroform extracts were used for CD, UV-visible, mass spectrometry and thin-layer chromatography studies. The structure of one of the products (Compound I) was determined by X-ray crystallography.

TABLE III

LIST OF COLOR TEST REAGENTS

Reagent	Composition	Color developed after a week
Froehde	700 mg of ammonium molybdate in 50 ml of concentrated sulfuric acid	dark purple to green
Mecke	250 mg of seleneous acid in 25 ml of concentrated sulfuric acid	dark brown to greenish gray
Mandelin	1 gm of ammonium vanadate in 100 ml concentrated sulfuric acid	dark brown purple

2. Apomorphine hydrochloride (20 mg) was added to 10 ml concentrated sulfuric acid and to 10 ml of Froehde reagent, respectively. The UV-visible and CD spectra of the solutions were recorded as a function of time. After equivalent times had lapsed, the solutions were diluted and extracted in the same manner as was described morphine sulfate in (1) and CD and UV-visible spectra of the solutions were recorded.

3. Thin-layer chromatography (TLC) was used as a technique to determine the number of components in the chloroform extracts. A mixture of chloroform, acetone,

methanol and dimethylamine in the ratio of 5:4:4:1 by volume was used as the eluant. A visual separation was confirmed and developed by UV light. The experiment was performed at 5 ± 2°C.

X-ray Structural Analysis

For X-ray structural determinations, a single crystal of morphine sulfate was obtained by the recrystallization of morphine sulfate from water. A methyliodide salt was also prepared by the reaction of excess methyl iodide with morphine free base, by refluxing in methanol for two hours. After cooling the solution in a refrigerator for 24 hours long needle-shaped crystal of morphine methyliodide formed. The crystals were recrystallized from water.

Single crystals of morphine sulfate, morphine methyliodide and Compound I were sealed in capillaries and mounted on the Syntex P3 automated diffractometer. Unit cell dimensions of the three crystals were determined by least squares refinement of the best angular position for fifteen independent reflections during normal alignment procedures. The data were collected at room temperature using a variable scan rate, a θ-2θ scan mode and a scan width of 1.2 A° below $K_{\alpha 1}$ and above $K_{\alpha 2}$ to a mixumum 2θ value at 116°. Backgrounds were measured at each side of the scan for a combined time equal to the total scan time. The intensities of three standard reflections were measured after every 97 reflections and the intensities of these

reflections showed less than 8% variation. Corrections for decomposition were considered to be unnecessary. Data were corrected for Lorentz and polarization effects.

The structures of morphine sulfate and morphine methyliodide were solved from the Patterson synthesis (39) to locate the heavy atoms. Successive least squares, difference Fourier cycles allowed for the location of the remainder of the non-hydrogen atoms. The unknown structure of Compound I was solved by direct methods using MULTAN80 (40).

Refinement of the scale factor, and positional (x, y, z) and anisotropic thermal parameters (U_{11}, U_{12}, U_{13}, U_{22} U_{33}, U_{23}) for all non-hydrogen atoms (41) was carried out to convergence. All hydrogen positional parameters of morphine methyliodide were determined from a difference Fourier synthesis. Positions of hydrogens on C6, C8 and C17 of morphine methyliodide, however, were calculated assuming normal geometry and a C-H distance of 0.97 A^{o}. These hydrogen positional parameters and the associated isotropic thermal parameter (U) of Compound I were refined along with non-hydrogen parameters in the final cycles of refinement. The hydrogen positional parameters of morphine sulfate were refined along with non-hydrogen parameters in the final cycles of refinement but the associated isotropic thermal parameters were assigned to be 0.03 and were held invariant. In the case of the methyliodide salt, all parameters associated with hydrogen

atoms were held invariant with the isotropic thermal parameter of U = 0.03.

The final cycle of refinement (function minimized $\Sigma(|F_{obs}| - |F_{cal}|)^2$) led to the ultimate agreement factor R defined as

$$R = (\Sigma \big| |F_{obs}| - |F_{cal}| \big|) * 100/\Sigma|F_{obs}|$$

Anomalous dispersion corrections were made for the iodide ion in the morphine methyliodide structure. Scattering factors for the elements were taken from Cromer and Mann (42). Unit weights were applied throughout the experiments.

Solid State Circular Dichroism Study of Morphine Methyliodide

The morphine methyliodide used in the previous section was used for a solid state circular dichroism (SSCD) study. The result was compared to the SSCD spectra for morphine free base and morphine sulfate reported earlier by Purdie and Bowen (31).

Samples for SSCD were prepared by pressing the morphine salt in KBr pellets formed in the usual way. Infrared grade KBr (Aldrich Chemical Co.) and the compound were dried at 110°C at least 48 hours prior to being pressed. A typical specimen consisted of approximately 0.8 mg of the salt in 80 mg KBr. The KBr pellet must be thin (ca. 0.2 mm) for adequate UV transmission.

The spectrum was taken on the instrument in the

normal manner with the sample supported in a holder constructed to fit both the pellet press and the carriage in the sample compartment of the CD instrument in order to avoid any damage to the fragile specimen. Tests for the existence of linear dichroism components to the signal were made by rotating the sample by various intervals from 0^{o} to 180^{o} and repeating the spectrum. The sample was dissolved in distilled water and an isotropic solution CD spectrum was obtained. Experiments were repeated for the SSCD of morphine free base and morphine sulfate to obtain spectra under the same conditions on the same instrument for a legitimate comparison of the results.

CHAPTER IV

EXPERIMENTAL RESULTS

Oxidation of Morphine in Basic Solution

Pseudomorphine is believed to be the first product formed from the oxidation of morphine by dissolved oxygen in basic solution as mentioned earlier. Although a dimer has been confirmed, its structure has not been established with any certainty, hence the reason for an X-ray structure analysis. Every attempt to produce suitable single crystals of either pseudomorphine or its derivatives failed, although a variety of solvents and experimental conditions were explored. Therefore NMR spectroscopy was used in order to obtain some structural information.

NMR Study of Pseudomorphine

A comparison of the ^{1}H NMR spectrum of pseudomorphine (Figure 9) with that for morphine sulfate (Figure 10) in DMSO(d6) shows a significant change in the region of the aromatic protons (δ = 6.2-6.6 ppm). The quartet observed for morphine sulfate reduces to a singlet for pseudomorphine. Integrations of these two spectra show that the relative numbers of hydrogen(s) under the quartet and the

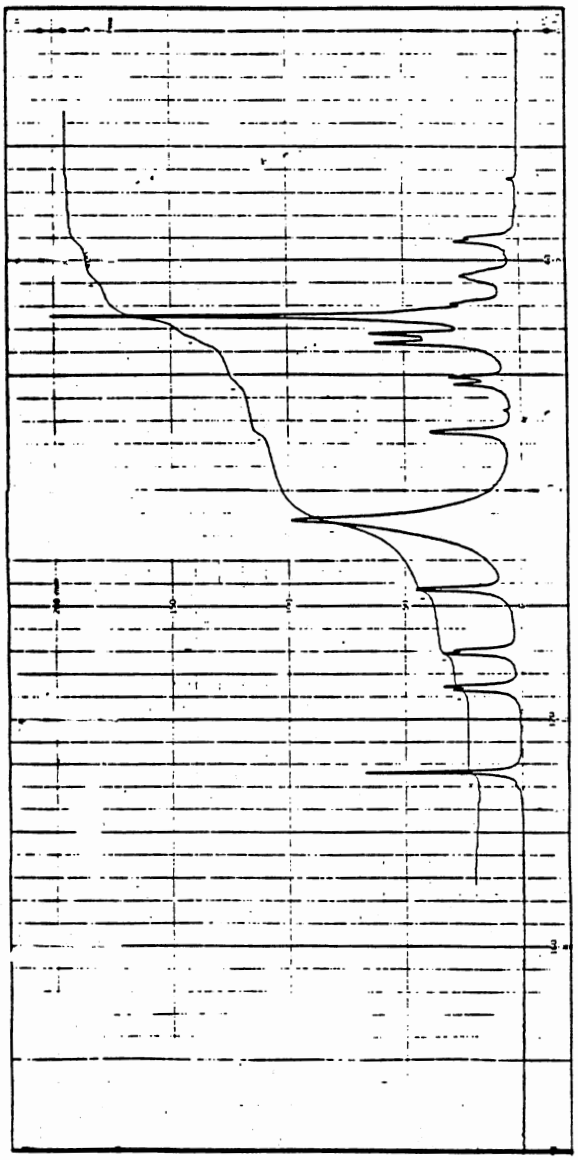


Figure 9. ^{1}H NMR Spectrum of Pseudomorphine in DMSO (d6)

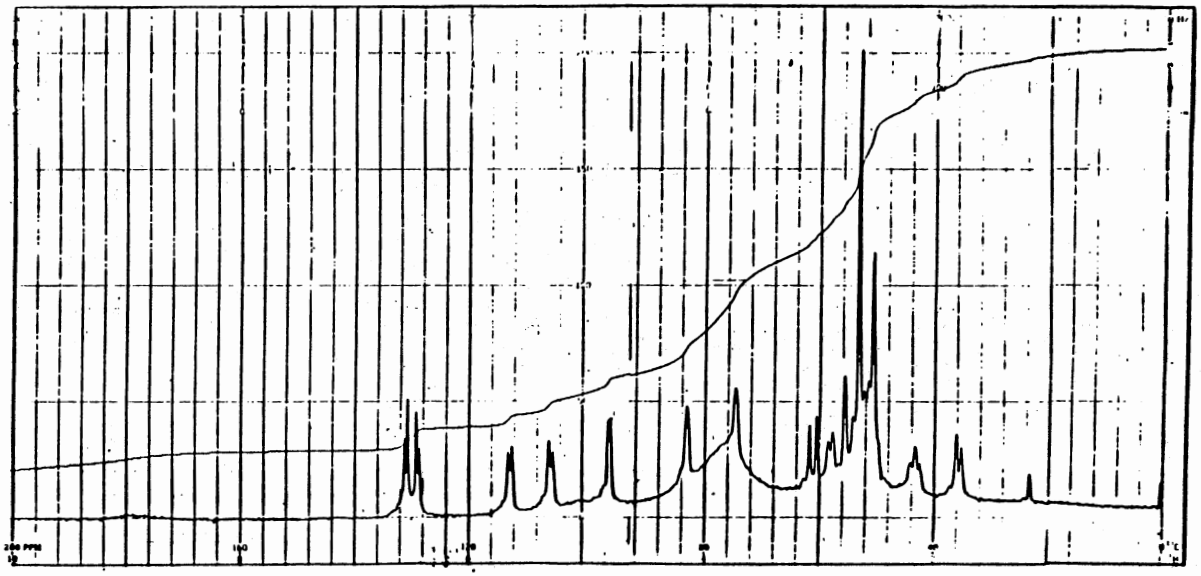


Figure 10. ^{1}H NMR Spectrum of Morphine Sulfate in DMSO (d6)

singlet are two and one for morphine sulfate and pseudomorphine, respectively. The remaining peaks in both spectra are quite similar.

The fully decoupled and off-resonance decoupled ^{13}C NMR spectra of pseudomorphine (Figures 11 and 12) on the other hand compare very well with those for morphine sulfate (Figures 13 and 14). The spectra show that both molecules are composed of seventeen different carbons, eight of which are unsaturated as expected. Chemical shifts for the unsaturated-carbon range from 119 to 150 ppm from the internal standard TMS. Assignments for the carbon chemical shifts for pseudomorphine (Table IV) were based on the equivalent assignments made for morphine sulfate. The latter assignments were made from data from the off-resonance experiments for morphine sulfate and codeine (Figure 15), as well as the fully decoupled spectrum for codeine (Figure 16). The carbon assignments for morphine sulfate were in accord with an earlier interpretation reported by Carroll, Moreland, Brine, and Kepler (43). Most of the carbon chemical shifts of pseudomorphine correspond with the analogous carbon chemical shifts for morphine sulfate to within ± 1 ppm, except for carbons C1, C2, C3, C11 and C12, which are the carbons directly affected by the dimerization of the two morphine molecules in producing the pseudomorphine structure. A reversal in the order of the C1 and C2 peaks for pseudomorphine compared to morphine

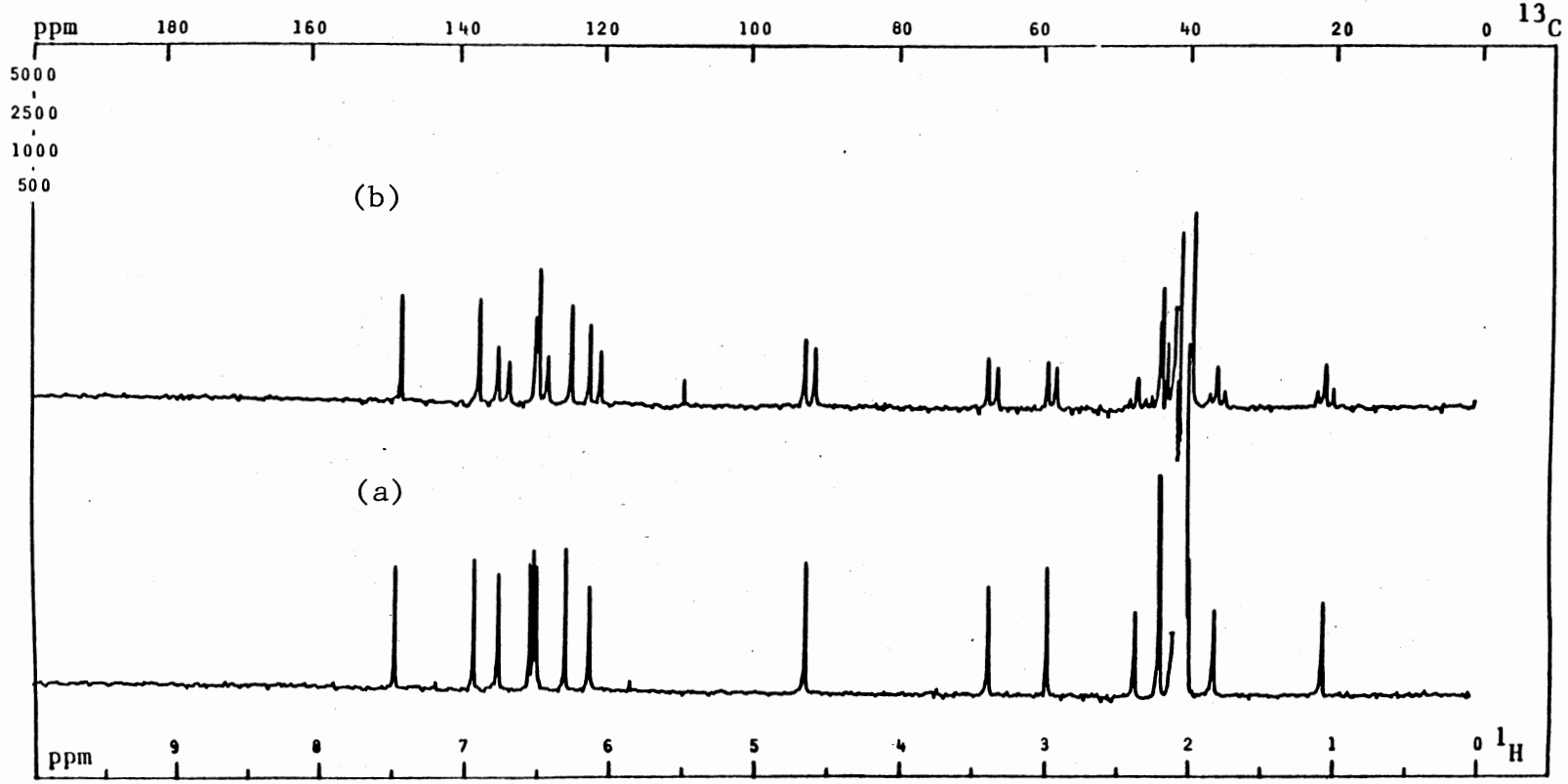


Figure 11. ^{13}C NMR Spectra of Pseudomorphine in DMSO (d6): a) Fully Decoupled, and b) Off-resonance

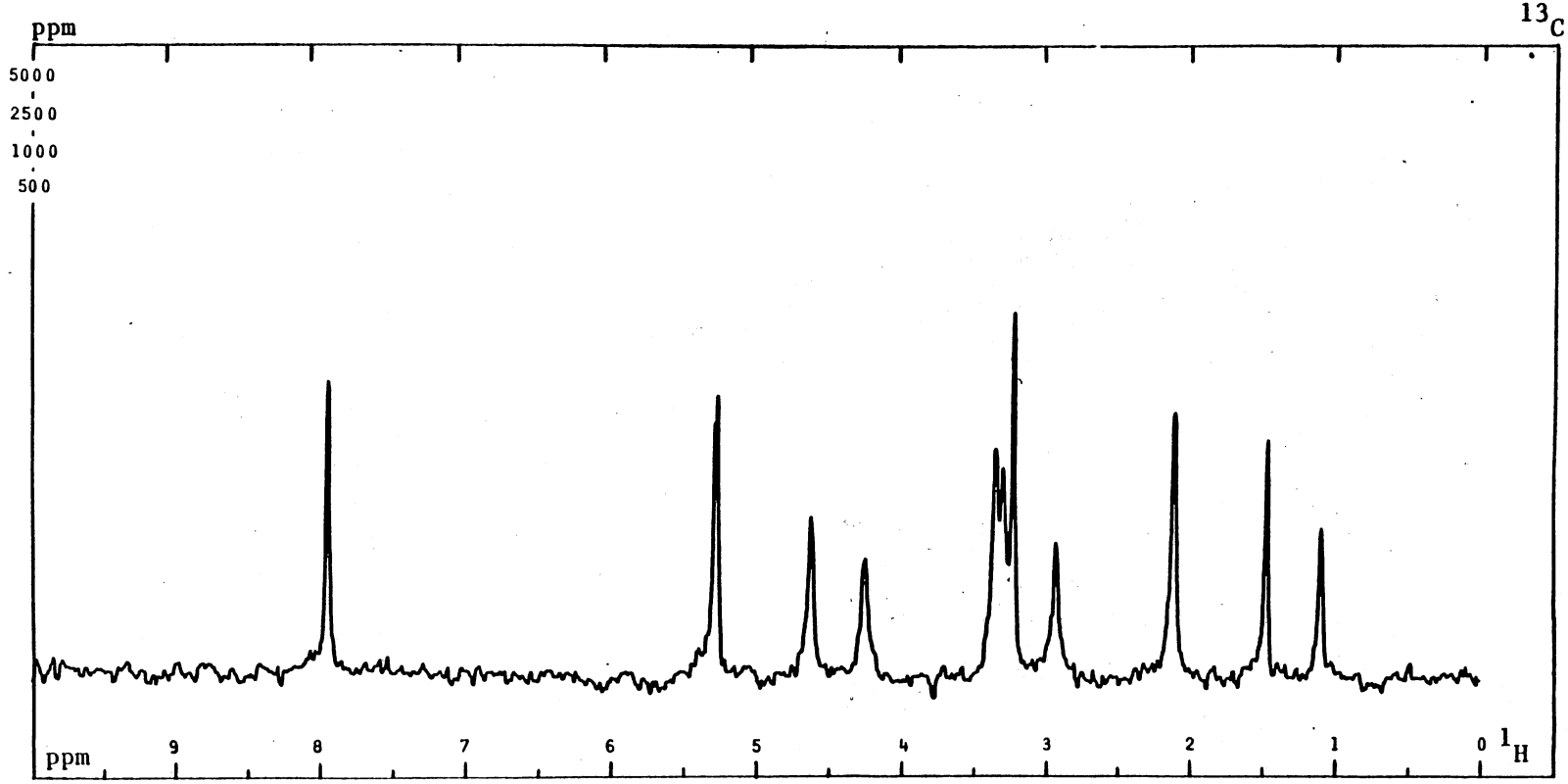


Figure 12. The Unsaturated Region Expansion of the Pseudomorphine ^{13}C Off-resonance NMR Spectrum

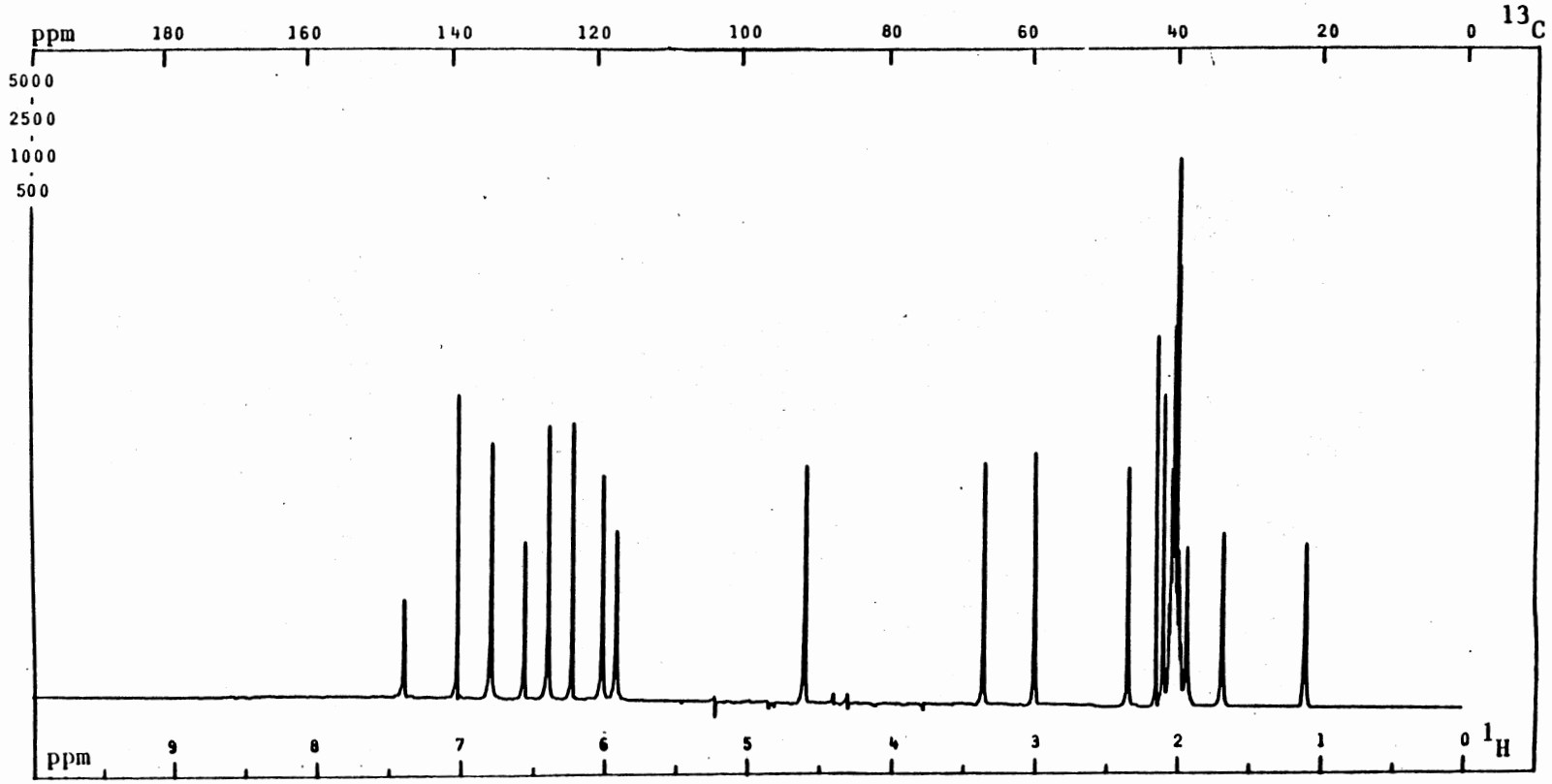


Figure 13. ^{13}C NMR (Fully Decoupled) Spectrum of Morphine Sulfate in DMSO (d6)

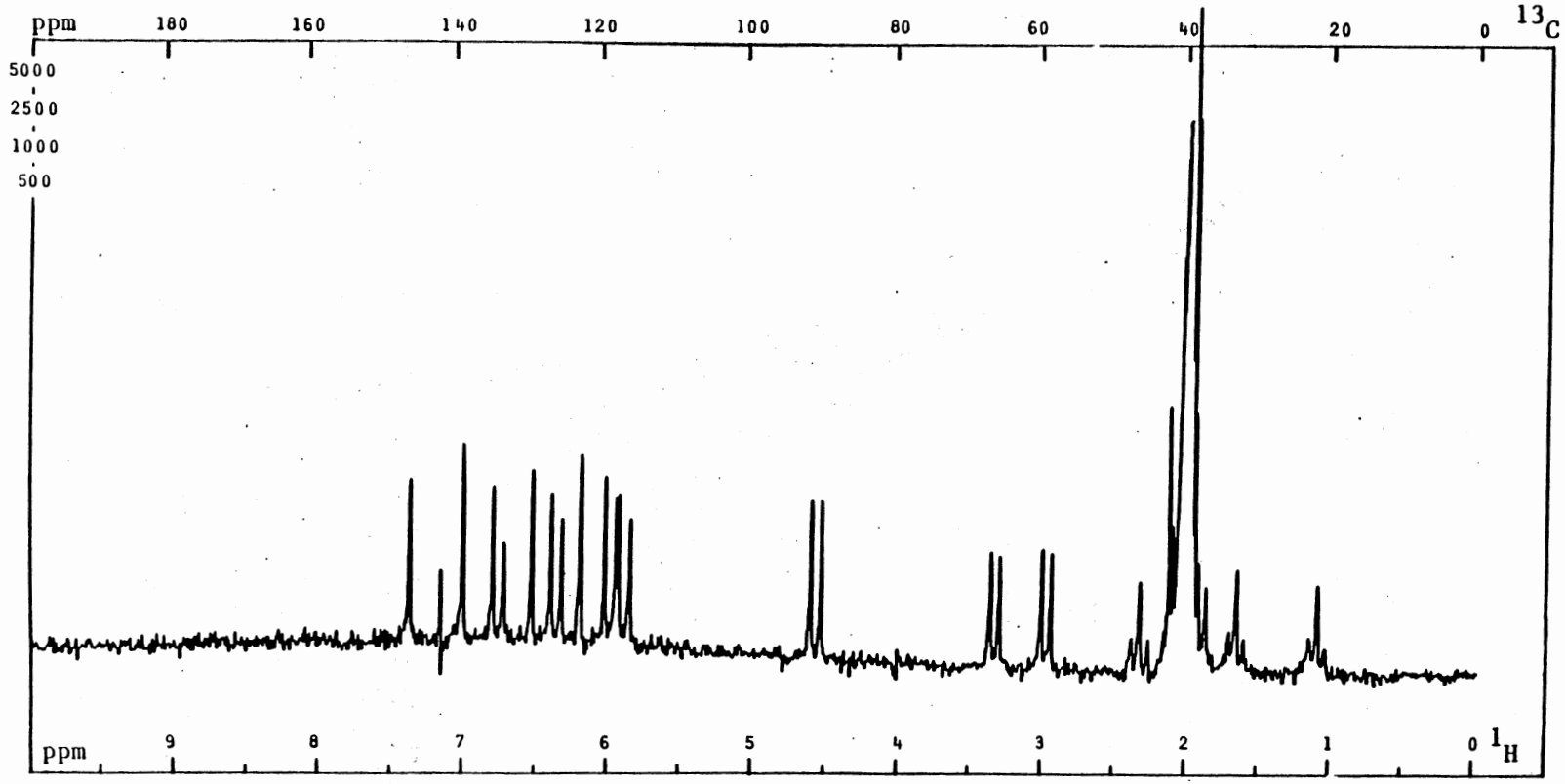


Figure 14. ^{13}C NMR (Off-resonance) Spectrum of Morphine Sulfate in DMSO (d6)

TABLE IV

^{13}C NMR CHEMICAL SHIFTS OF MORPHINE SULFATE AND PSEUDOMORPHINE IN DMSO (d6)

Identification Carbon	Chemical Shifts (ppm) from TMS	
	Morphine Sulfate	Pseudomorphine
1	119.05	121.0
2	117.10	124.3
3	139.10	136.9
4	146.40	147.5
5	90.90	91.7
6	66.20	66.4
7	134.40	133.5
8	128.70	128.5
9	58.10	58.2
10	20.20	20.3
11	125.50	128.3
12	131.04	129.2
13	42.97	42.7
14	40.63	40.3
15	35.60	35.2
16	46.05	46.0
17	42.83	42.6

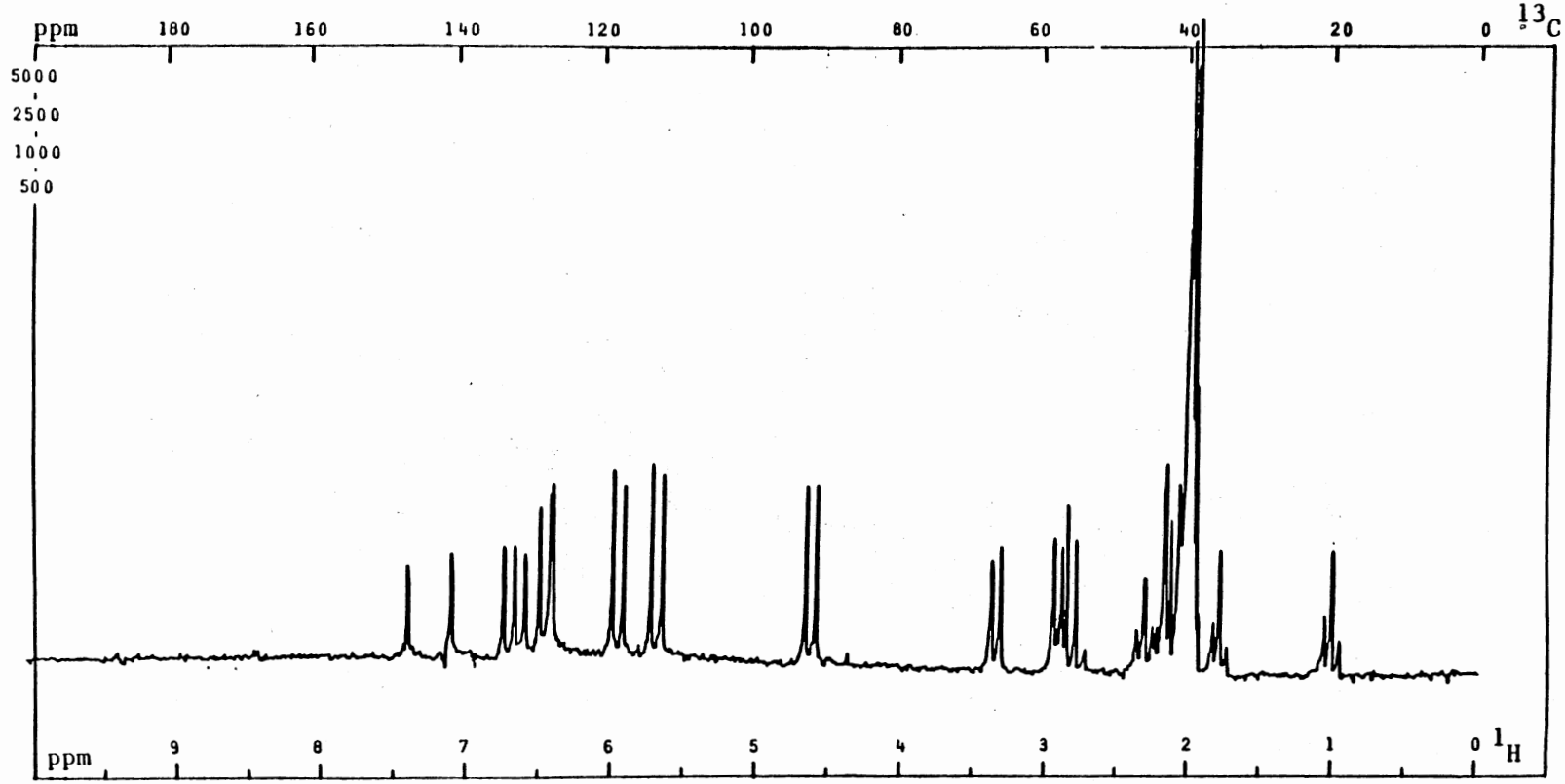


Figure 15. ^{13}C NMR (Off-resonance) Spectrum of Codeine in DMSO (d6)

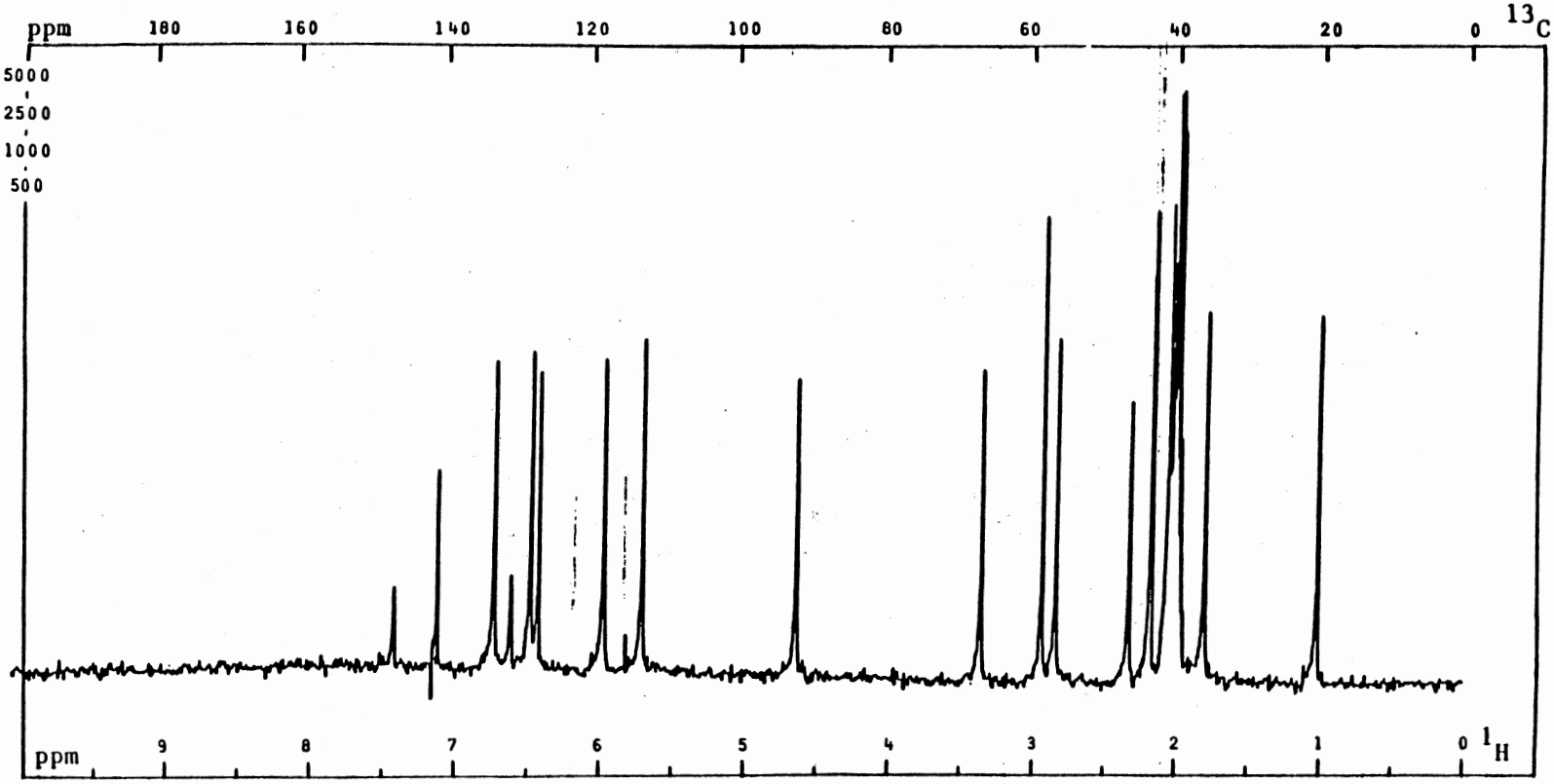


Figure 16. ^{13}C NMR (Fully Decoupled) Spectrum of Codeine in DMSO (d6)

sulfate is suggested and supported by the comparison of the results with chemical shift data among monomers and dimers of two pairs of model compounds, phenol (Figures 17, 18), o,o'-biphenol (Figures 19, 20) and anisol (Figures 21, 22) and 3,3'-bianisole (Figures 23, 24). Chemical shift data for the model compounds are listed in Table V and Table VI. The chemical shifts assignments for phenol and anisole were based on the values reported in the Atlas of Carbon-13 NMR Data (43).

Oxidation of Pseudomorphine in Base

Pseudomorphine is not oxidized by air on standing in basic solutions (concentrated ammonium hydroxide or .2% KOH). However, pseudomorphine as the potassium salt is quickly oxidized to an unidentified higher oxidation product (HOP) on the addition of an excess of 1% solution of $KMnO_4$ which is decolorized in the reaction. The dark brown precipitate of MnO_2 is formed and the solution turns light brown in color. Evidence for a new compound is apparent from the changes which occur in the CD spectrum of pseudomorphine (Figure 25). The positive Cotton band whose maximum occurs at 320 nm for pseudomorphine is absent for HOP and the 275 nm negative maximum is shifted to the shorter wavelength at 263 nm. The CD spectral characteristics for morphine, pseudomorphine and HOP are presented in Table VII for easy comparison.

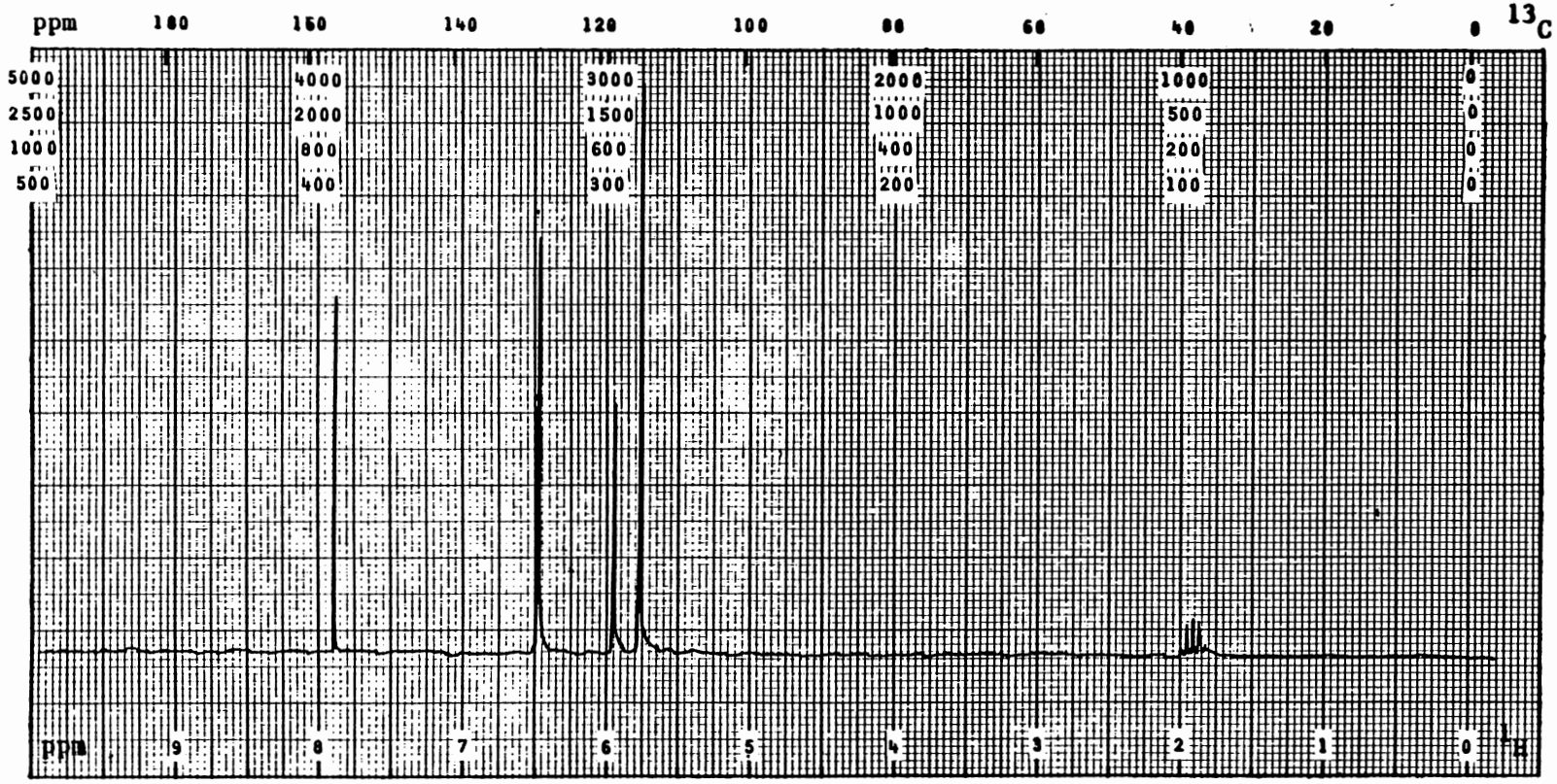


Figure 17. ^{13}C NMR (Fully Decoupled) Spectrum of Phenol in DMSO (d6)

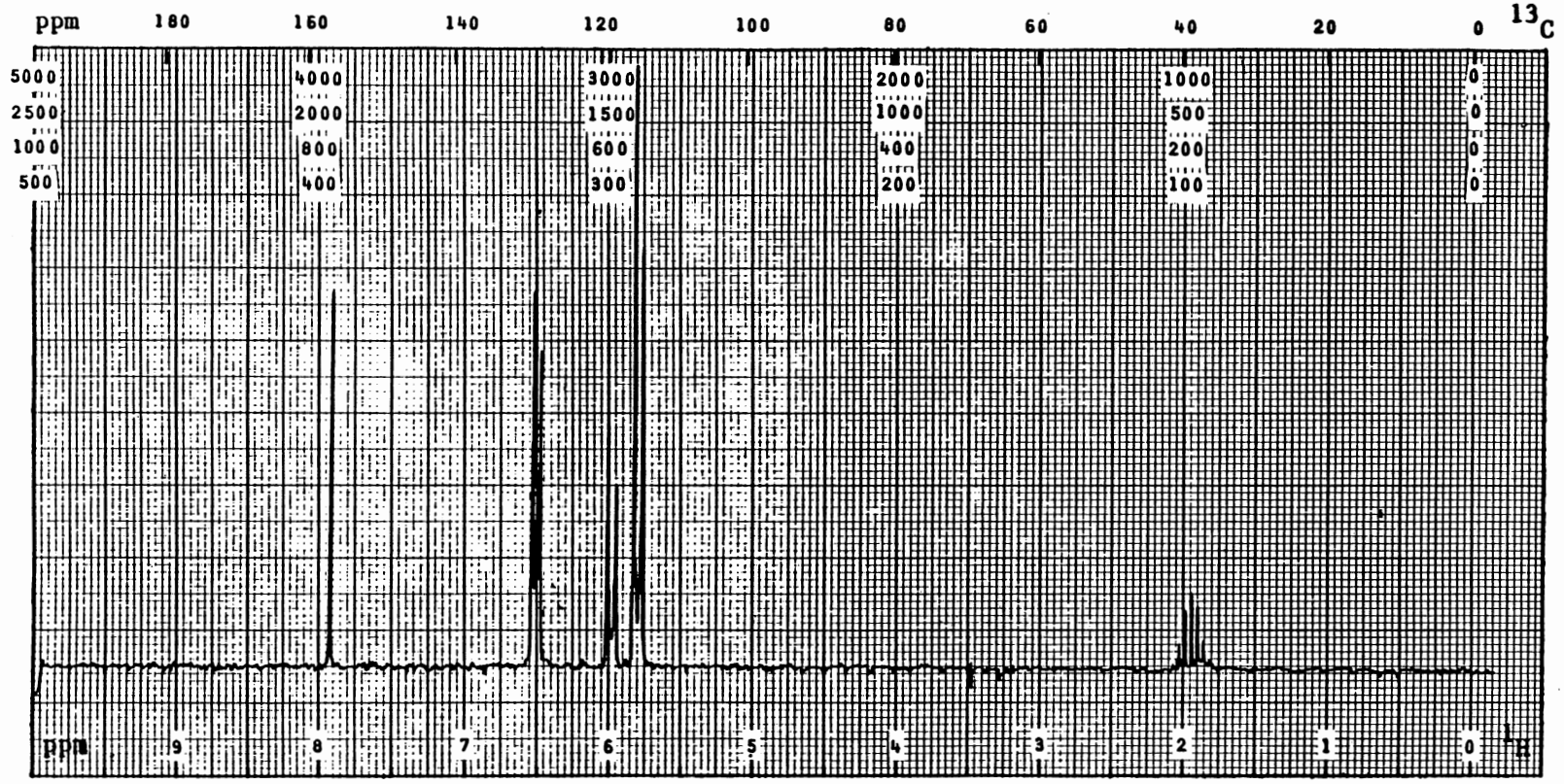


Figure 18. ^{13}C NMR (Off-resonance) Spectrum of Phenol in DMSO (d6)

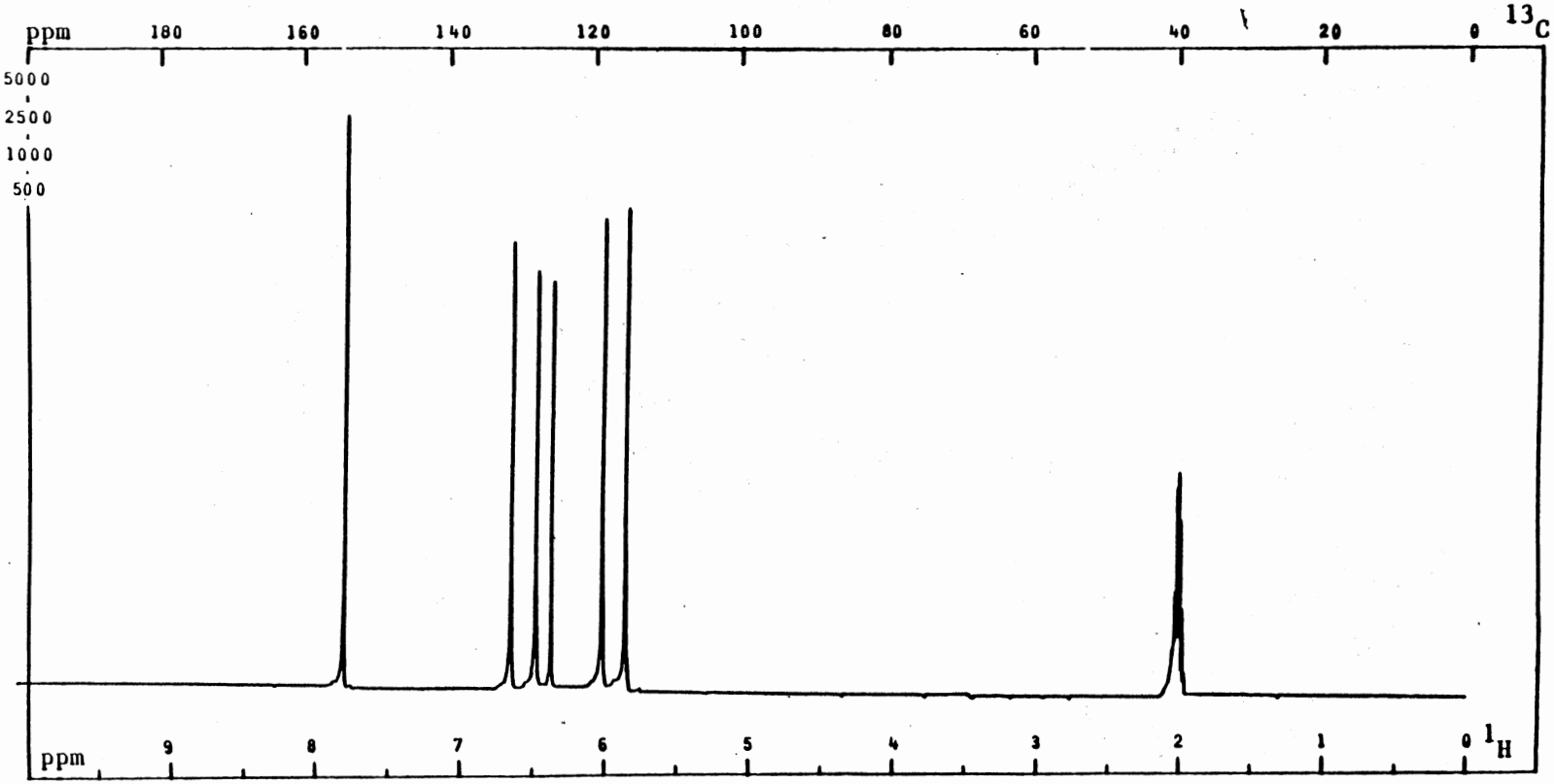


Figure 19. ^{13}C NMR (Fully Decoupled) Spectrum of o,o'-Biphenol in DMSO (d6)

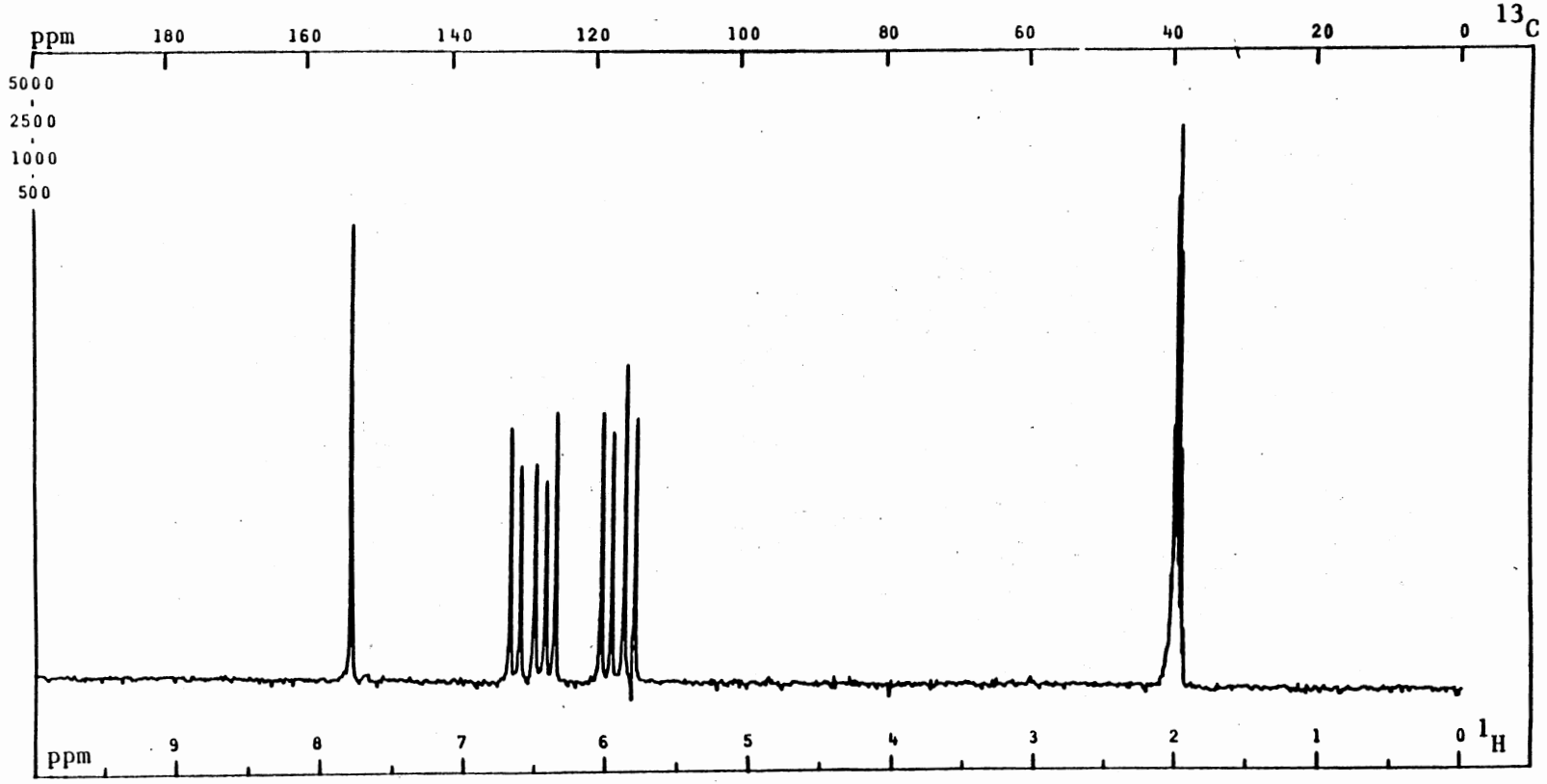


Figure 20. ^{13}C NMR (Off-resonance) Spectrum of o,o'-Biphenol in DMSO (d6)

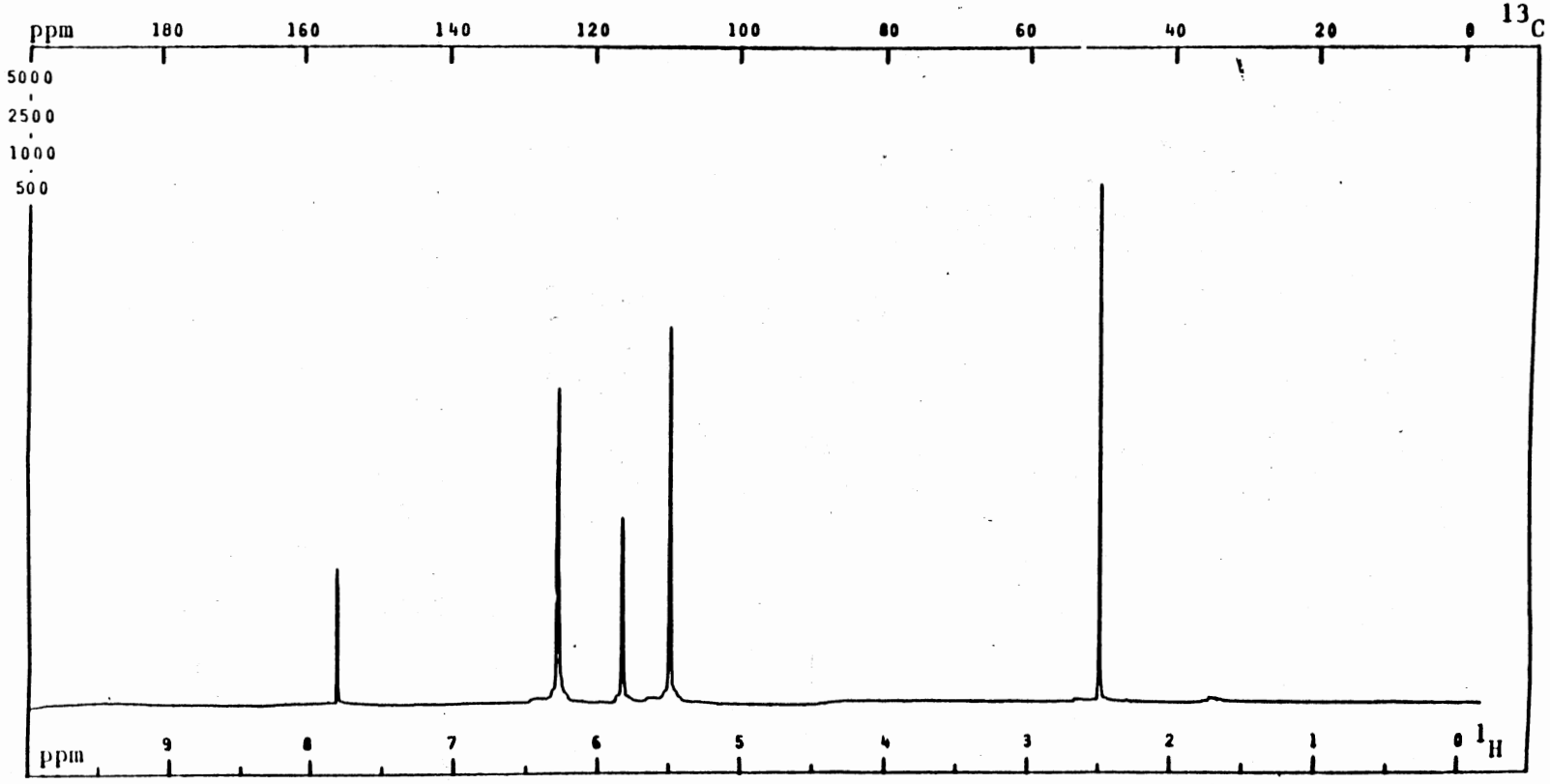


Figure 21. ^{13}C NMR (Fully Decoupled) Spectrum of Anisole in DMSO (d6)

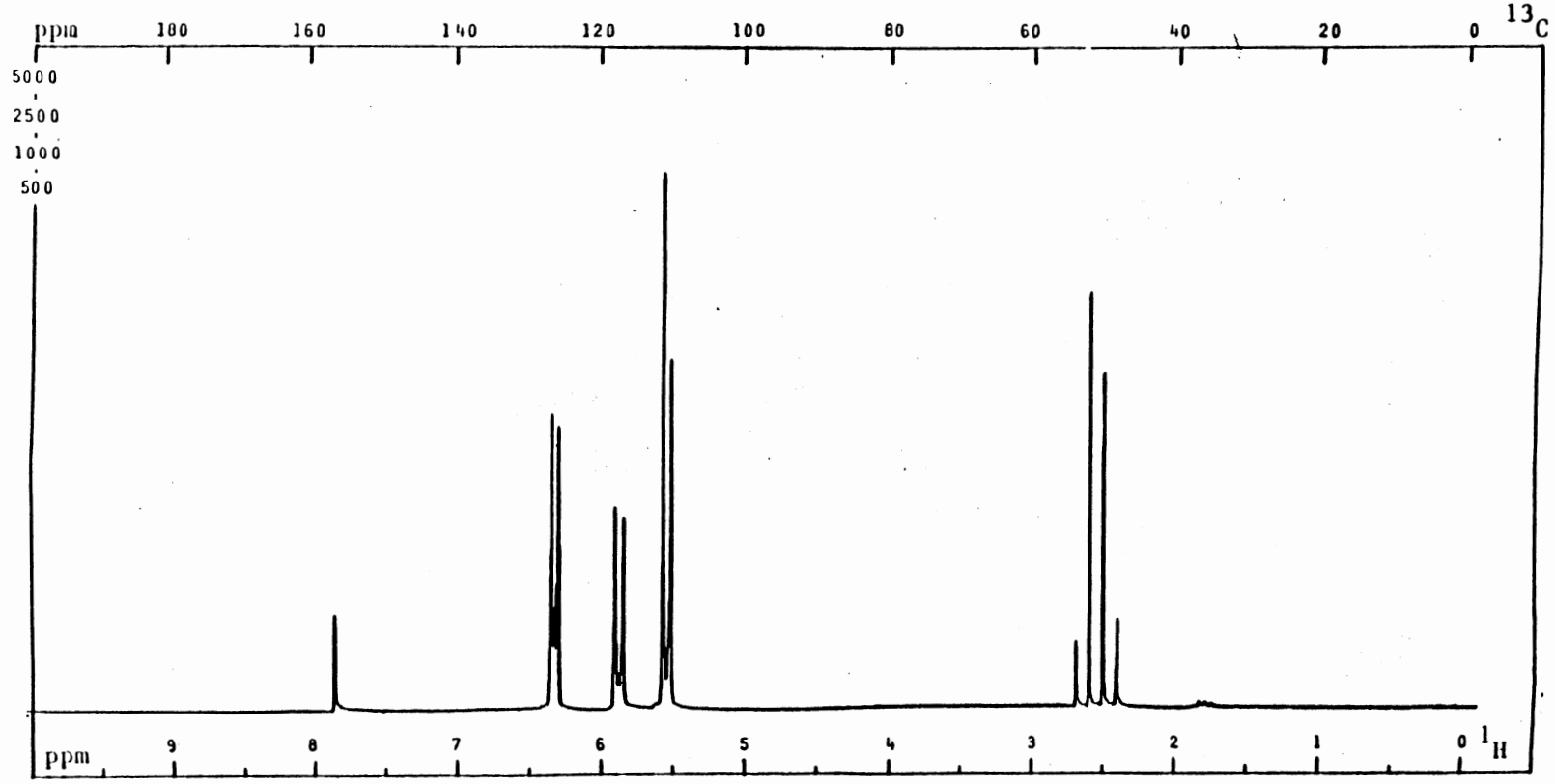


Figure 22. ^{13}C NMR (Off-resonance) Spectrum of Anisole in DMSO (d6)

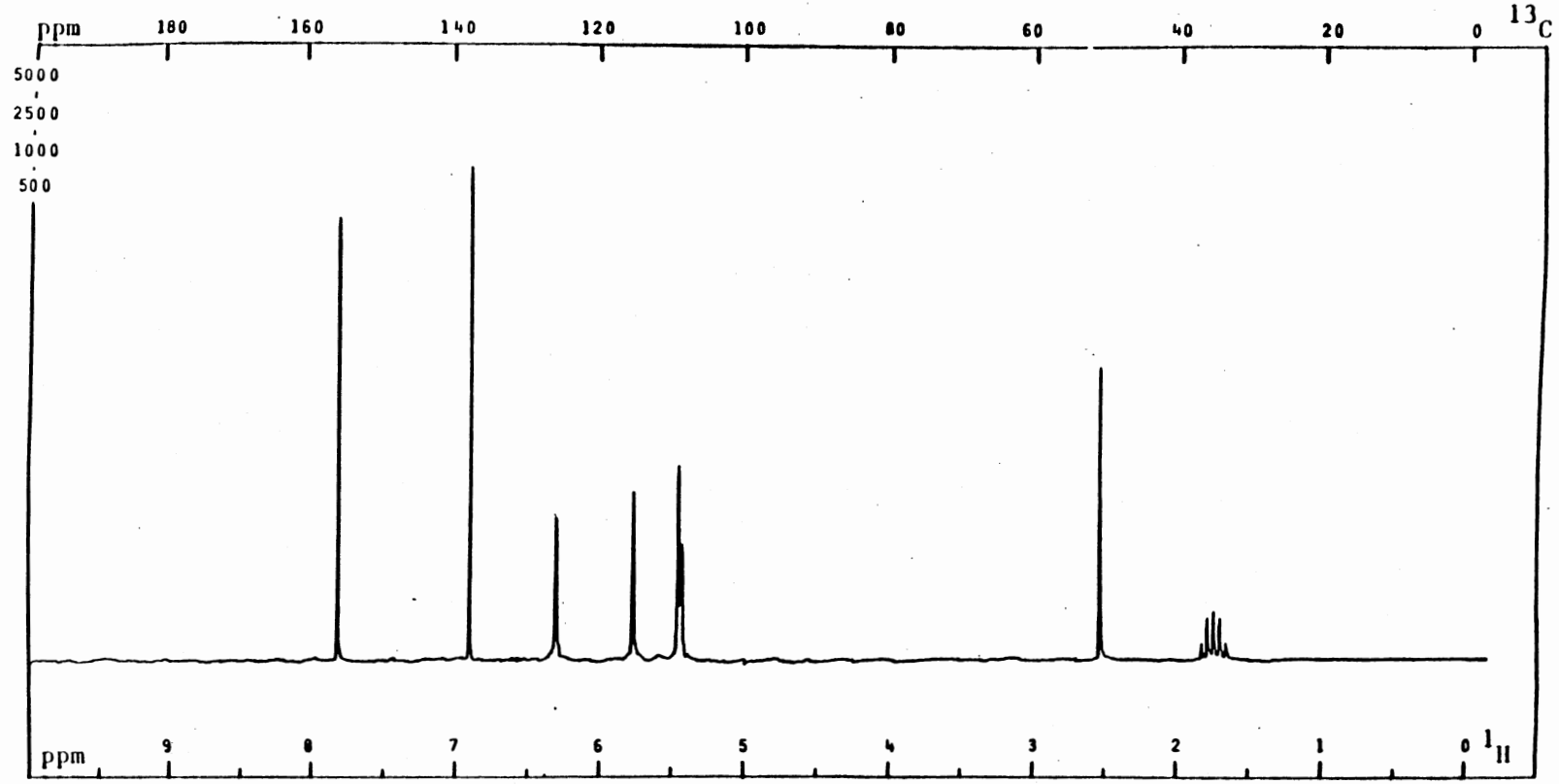


Figure 23. ^{13}C NMR (Fully Decoupled) Spectrum of 3,3'-Bianisole in DMSO (d6)

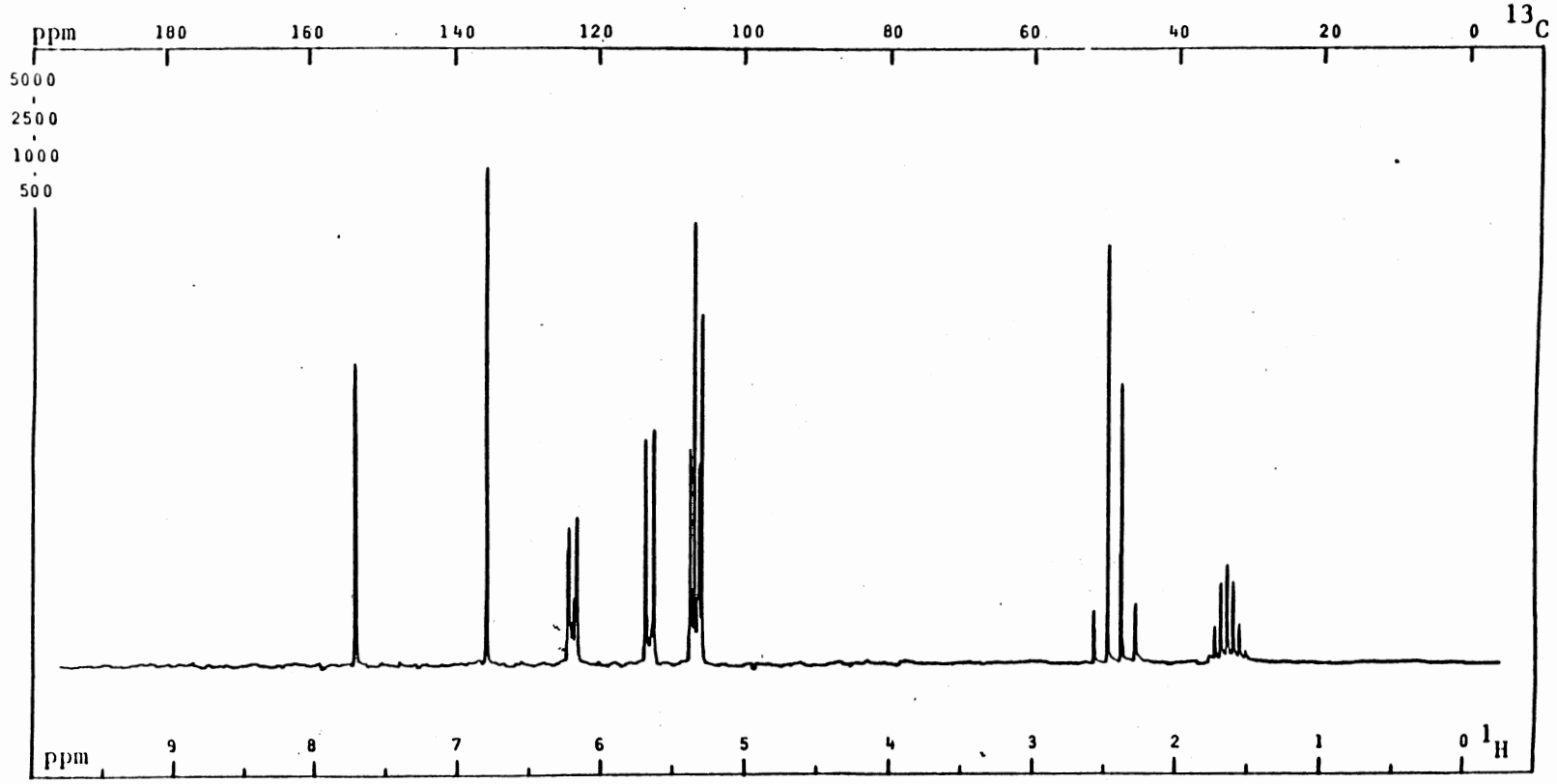


Figure 24. ^{13}C NMR (Off-resonance) Spectrum of 3,3'-Bianisole in DMSO (d6)

TABLE V

^{13}C NMR CHEMICAL SHIFTS OF PHENOL AND o,o'-BIPHENOL IN DMSO (d6)

Identification Carbon	Chemical Shifts (ppm) from TMS	
	Phenol	o,o'-Biphenol
1	157.516	154.530
2	115.750	126.026
3	129.562	131.624*
4	119.140	118.986
5	129.562	128.179*
6	115.750	115.843

*May be interchanged.

TABLE VI

^{13}C NMR CHEMICAL SHIFTS OF ANISOLE AND 3,3'-BIANISOLE IN DMSO (d6)

Identification Carbon	Chemical Shifts (ppm) from TMS	
	Anisole	3,3'-Bianisole
1	155.487	155.608
2	109.731	108.377
3	125.257	137.606
4	116.303	115.049
5	125.257	125.782
6	109.731	108.861
7	50.406	50.937

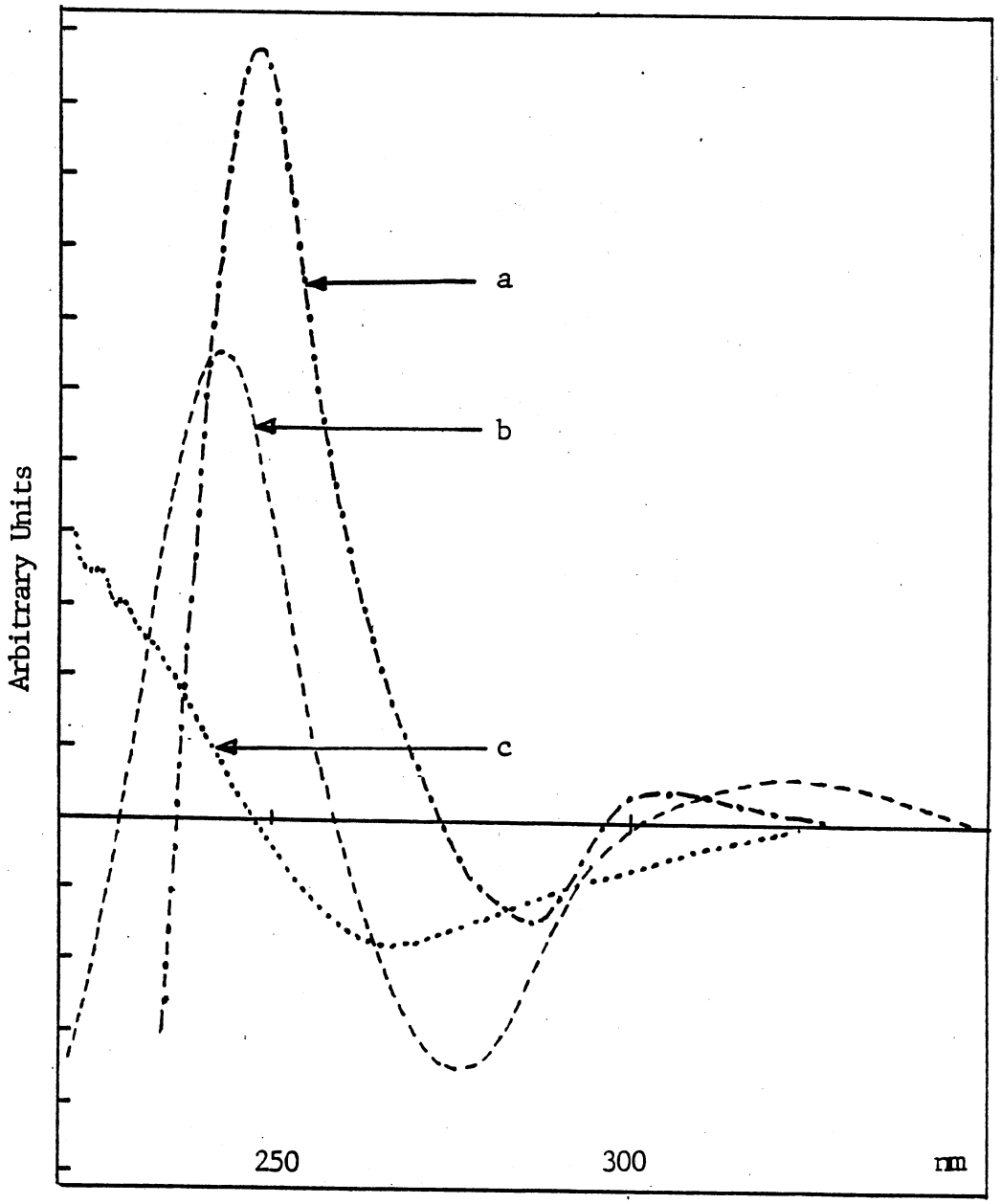


Figure 25. CD Spectra of a) Morphine in Distilled Water, b) Pseudomorphine in Distilled Water, and c) Oxidation Product of Pseudomorphine in Distilled Water

TABLE VII

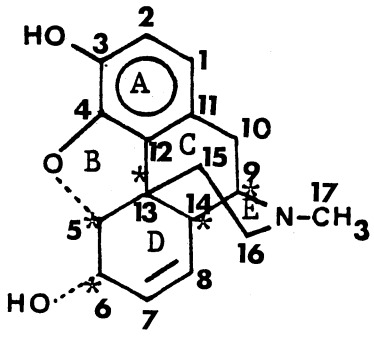
CD DATA OF MORPHINE, PSEUDOMORPHINE AND HOP IN DISTILLED WATER

Compound	λ^{+}_{max} (nm)	λ^{-}_{max} (nm)	λ^{o} (nm)
Morphine	303, 247	285	296, 270, 236.5
Pseudomorphine	320, 243	274-5	303, 259, 229
HOP	—	263	247

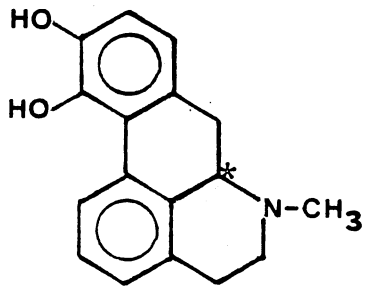
Oxidation of Morphine and Pseudomorphine by Metal Ions in Neutral Solution

A number of simple ions and two complex metal ions were used as potential oxidizing agents for morphine and pseudomorphine in neutral solutions. Evidence for new products was obtained from a CD study since both alkaloids and the possible products are CD active (Figure 26).

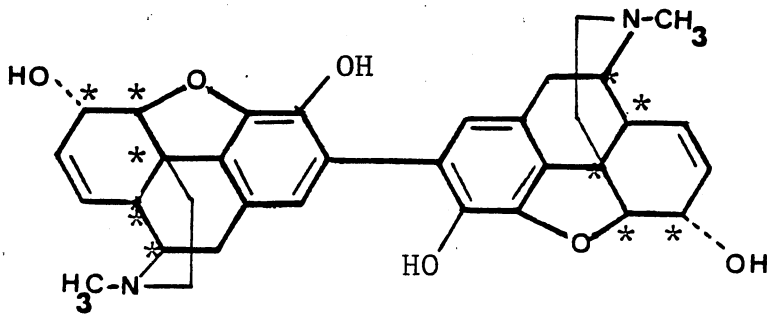
The oxidation of morphine to pseudomorphine is rapid when the mole-ratio of silver ion to morphine is 3:1 or higher. Within seven days the CD spectra (Figure 27) of the solutions correspond with the CD spectrum for HOP described for the basic $KMnO_4$ reaction. Reduced silver is deposited on the wall of the containers. At lower mole-ratios (1:1 and 1:2), the oxidation appeared to terminate at pseudomorphine after 24 hours (Figure 28) and no evidence for the formation of HOP was found even though the solutions were allowed to stand at room temperature for one week. In excess $KMnO_4$ and $K_3Fe(CN)_6$, morphine was immediately oxidized to pseudomorphine and subsequently more slowly to HOP with time (Figure 29). For the metal ions, copper(II), lead(II), nickel(II), cadmium(II) and zinc(II), there were no significant changes in the CD spectrum of morphine even after the solutions were kept at room temperature for a week. When pseudomorphine was used as a reducing agent, instead of morphine, it was found that the pseudomorphine was oxidized to the HOP in



Morphine



Apomorphine



Pseudomorphine

Figure 26. Structures of Morphine, Apomorphine and Pseudomorphine. (* Indicates chiral carbon.)

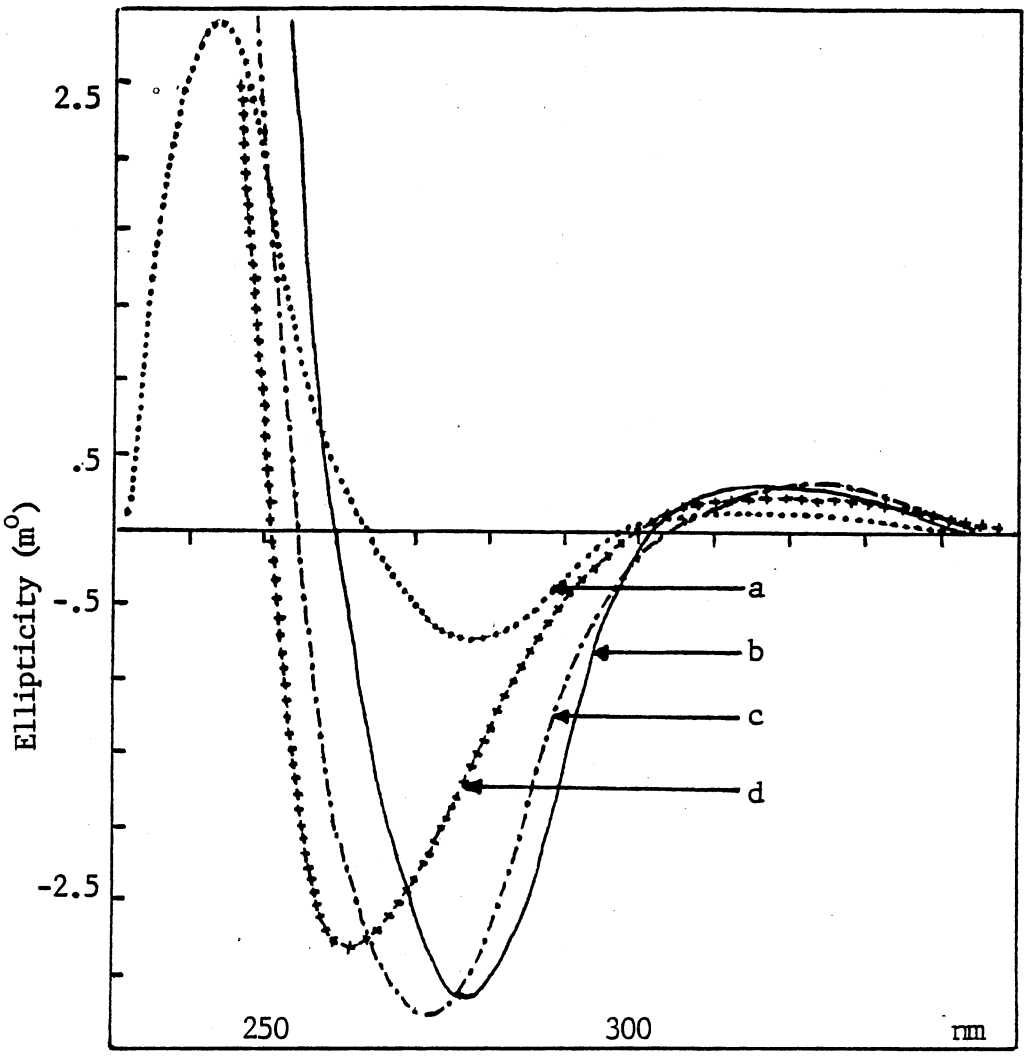


Figure 27. CD Spectra of Solutions from Ag^{+}-morphine at Mole-ratio 3:1 at Different Times. a) After mixing; b) After 15 minutes; c) After 24 hours; d) After a week.

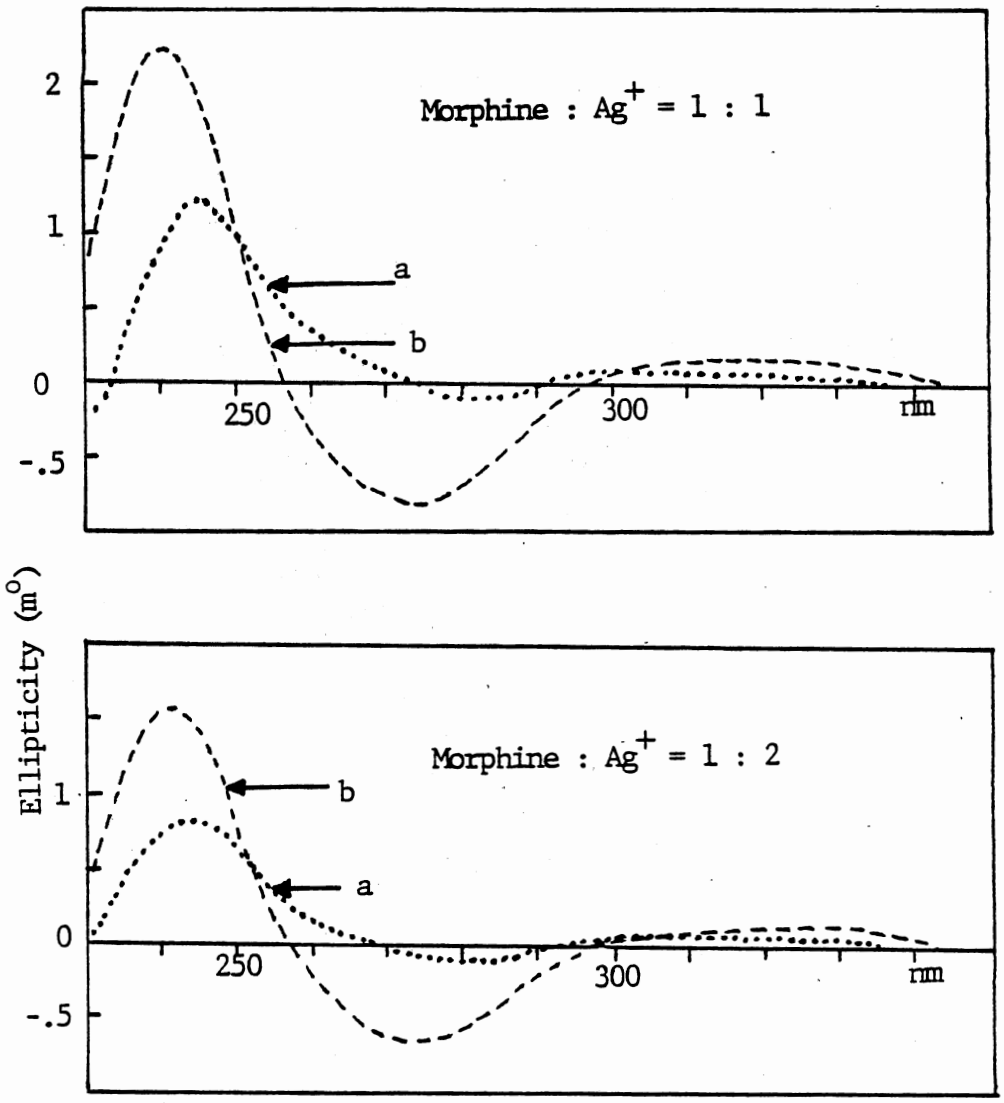


Figure 28. CD Spectra of Solutions from Ag^{+}-Morphine Reaction at Different Times. a) After Mixing, and b) After 24 Hours

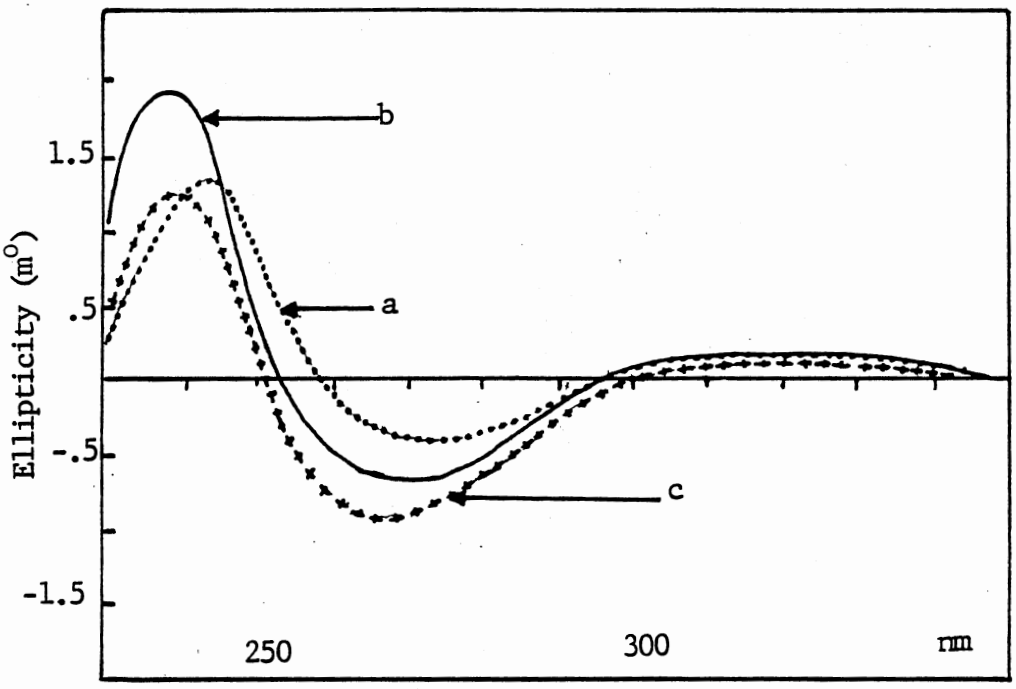


Figure 29. CD Spectra of Solutions from Morphine in Excess of $K_3Fe(CN)_6$ in Distilled Water. a) After mixing; b) After 1.5 hours; c) After 3 days.

excess of silver(I) ion, copper(II) ion, $KMnO_4$ and $K_3Fe(CN)_6$ (Figure 30) but not with lead(II), nickel(II), cadmium(II) and zinc(II) salts.

Oxidation of Morphine and Apomorphine in Strong Acid Solutions

Morphine Sulfate

When morphine sulfate was added to concentrated sulfuric acid and kept in air at room temperature, the color of the solution changed with time. At the outset the color of the solution of morphine sulfate in concentrated sulfuric acid is brownish-orange. The UV-visible spectra (Figures 31, 32) show four bands with wavelengths maxima at 210, 240, 270 and 450 nm. The relative intensities of the bands around 240 and 270 nm changed with time showing a decrease for the 240 nm band and an increase for the 270 nm band. Simultaneously the band maxima shifted to longer wavelengths. At the same time the 450 nm band was observed to diminish and a shoulder to the band at 400 nm appeared. The data as a function of time are summarized in Table VIII.

CD spectra of an identical solution (Figure 33) were recorded over the same time frame; that is, immediately after mixing and at intervals over the next sixteen days before a chloroform extraction was performed. The CD spectrum of morphine in concentrated sulfuric acid is

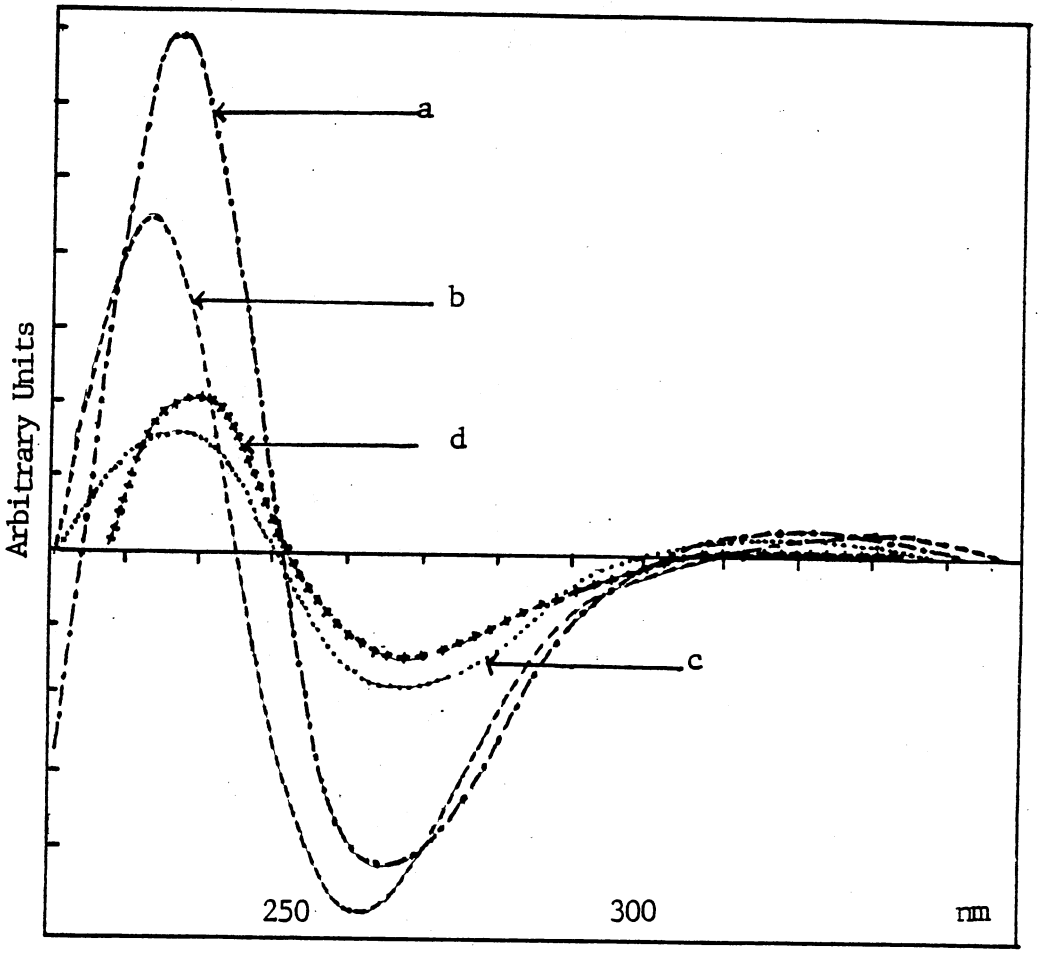


Figure 30. CD Spectra of Solutions Containing 1:10 Mole Ratio of Pseudomorphine to a) Cu^{+2} 2 Days After Mixing; b) Ag^{+} 2 Days After Mixing; c) $KMnO_4$ After Mixing; d) $K_3Fe(CN)_6$ After Mixing.

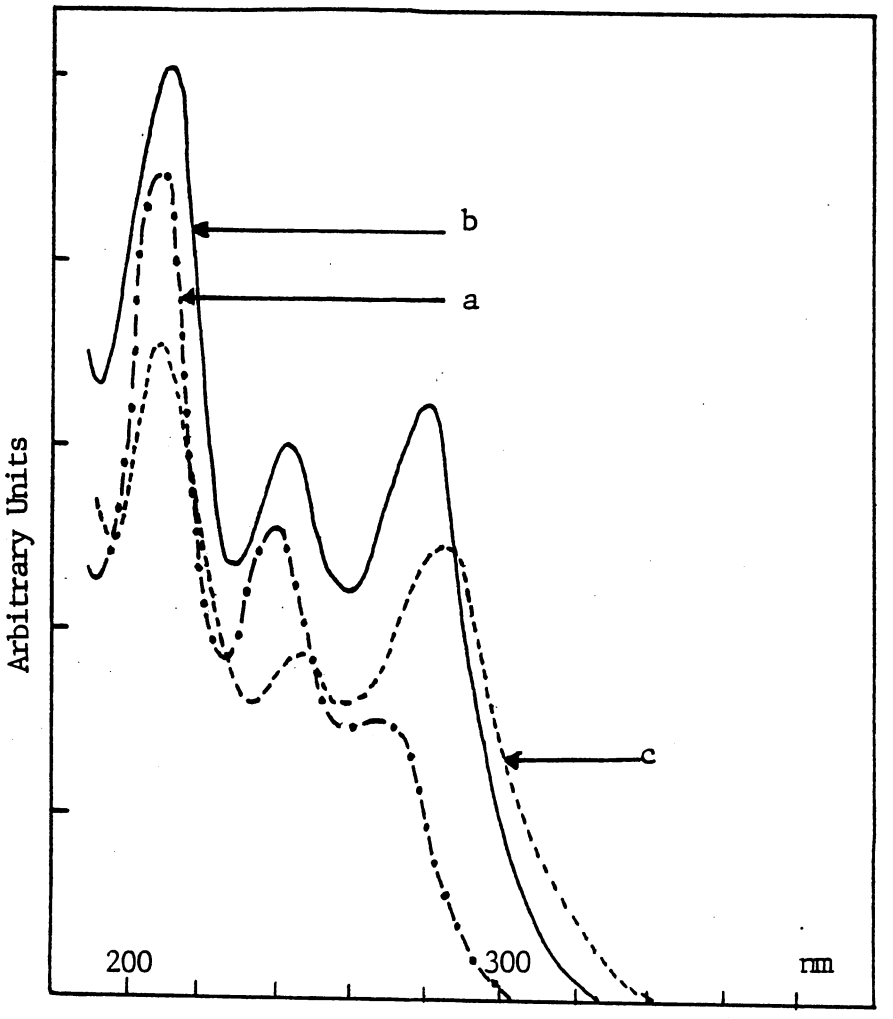


Figure 31. UV Spectra of Morphine Sulfate in Concentrated Sulfuric Acid.
a) After Mixing, b) After Standing at Room Temperature for 2 Days;
c) After Standing at Room Temperature for 16 Days.

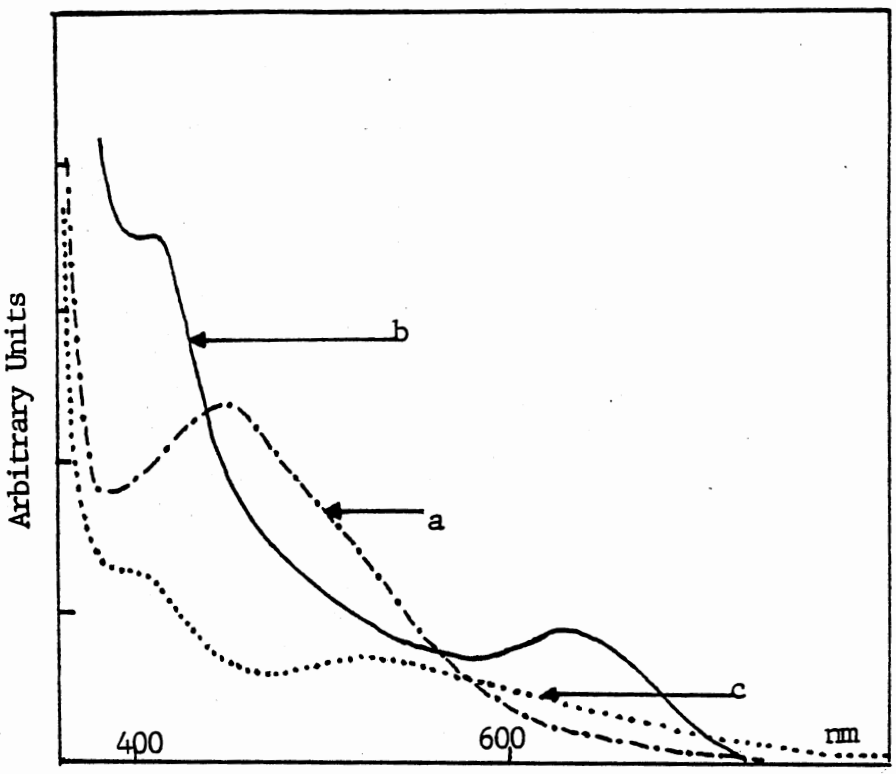


Figure 32. Visible Spectra of Morphine Sulfate in Concentrated Sulfuric Acid. a) After Mixing, b) After Standing at Room Temperature for 2 Days, c) After Standing at Room Temperature for 16 Days.

TABLE VIII

UV-VISIBLE DATA OF MORPHINE SULFATE IN CONCENTRATED SULFURIC ACID

Time Interval	Color Observed	λ_{max} (nm)
0	brownish-orange	210, 240, 270, 450
2 days	green	210, 242, 278, 400^{sh}
		635
16 days	brownish-gray	210, 245, 285, 400^{sh}
		520
1 month	brownish-purple	—

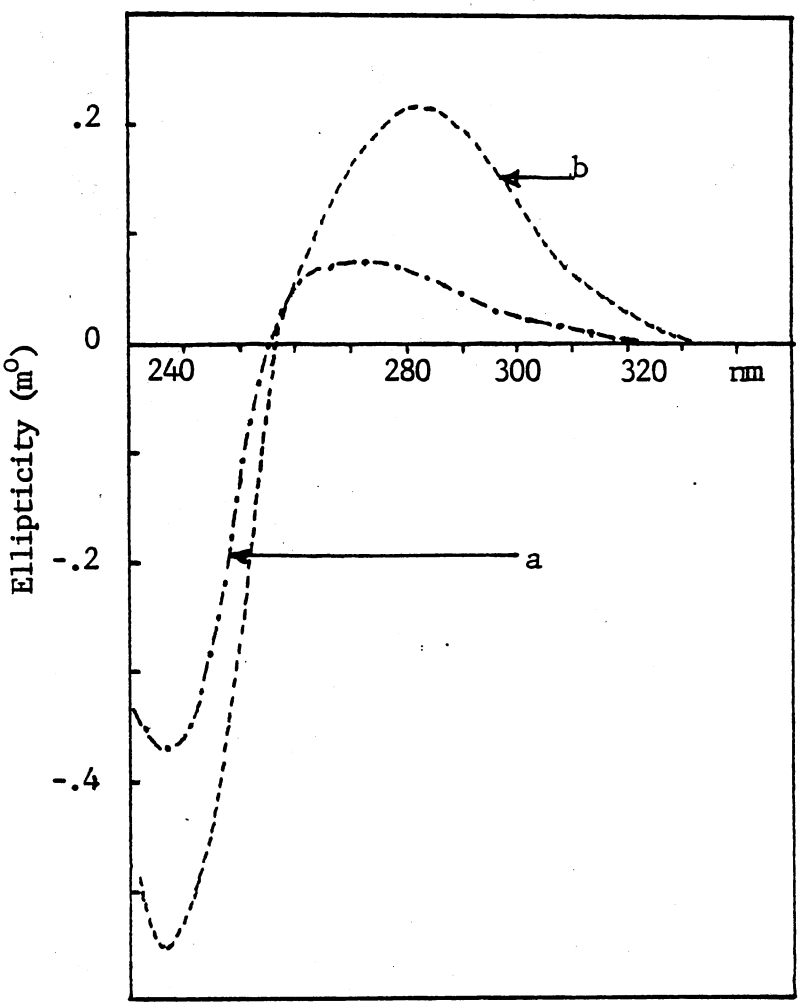


Figure 33. CD Spectra of Morphine Sulfate in Concentrated Sulfuric Acid. a) After Mixing; b) After Standing at Room Temperature for 16 Days

inverted from the spectrum in aqueous solution. Maxima occur at 270 nm (λ^{+}_{max}) and at 236 nm (λ^{+}_{max}). Dilution with water did not restore the spectrum to that in aqueous acid which confirms that an irreversible reaction has occurred on solution (45). The λ^{+}_{max} of the acid solution was observed to shift from 270 nm to 282 nm and λ^{o} from 255 nm to 257 nm with time.

When the color test reagents of Froehde, Mandelin and Mecke which contain the Mn(VI), V(V) and Se(IV) oxidation states in complex oxyanions dissolved in concentrated sulfuric acid are used instead of just the acid, the color changed to be either dark blue-green or dark blue within one hour. UV-visible and CD spectra for these solutions were reported previously by Ketkeaw (45). Some contribution to the color of the final product could arise from the reduced forms of the oxyanions.

The chloroform extracts of these solutions in contrast were purple or purple-blue in color. Presumably inorganic salts were not extracted. The aqueous layer after extraction was green. The UV-visible spectra (Figure 34, 35) for all of the chloroform extracts are similar with λ_{max} at 570, 310 and 238 nm which is indicative of a common product or mixture of products. No CD spectrum was observed for the chloroform extract solutions.

A mass spectrum (Figure 36) of the morphine-Froehde extract shows that the maximum molecular ion has a mass equal to 325.25 g/mole.

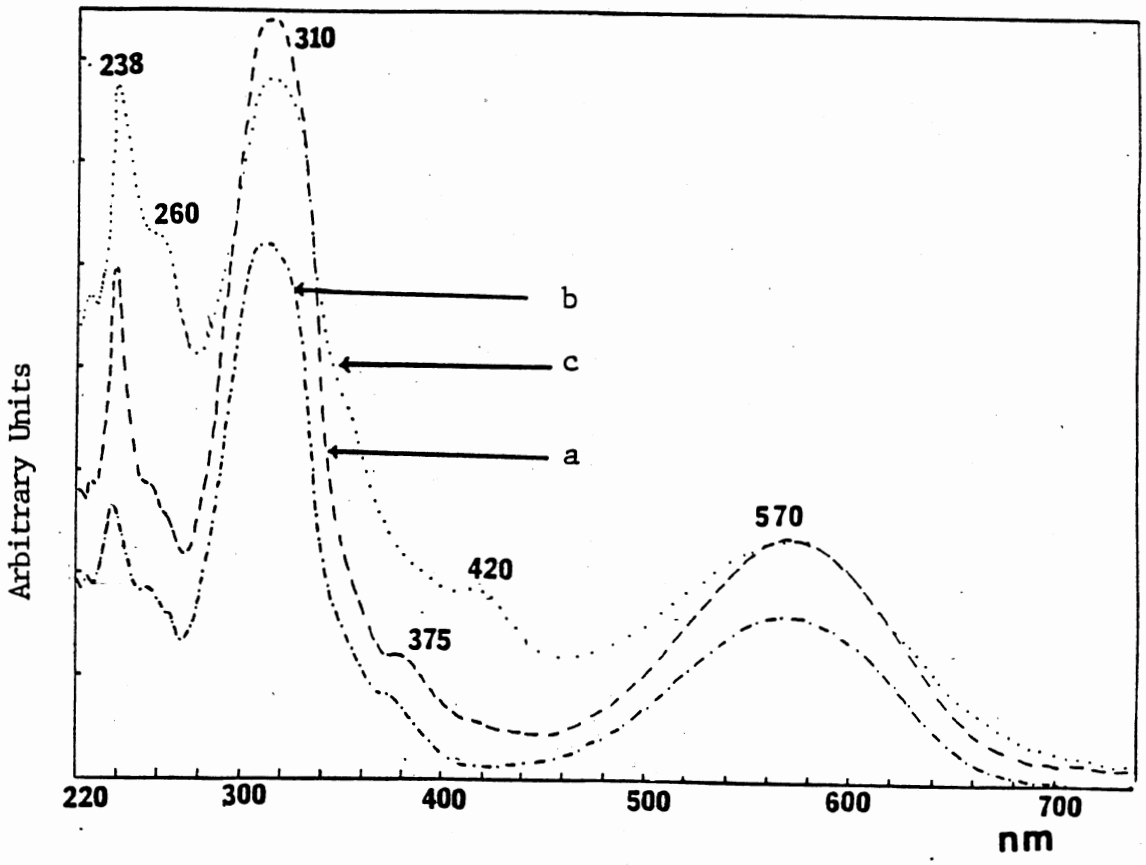


Figure 34. UV-visible Spectra of the Chloroform Extracts of the Solutions Containing Morphine Sulfate with a) Froehde Reagent, b) Mandelin Reagent, and c) Mecke Reagent.

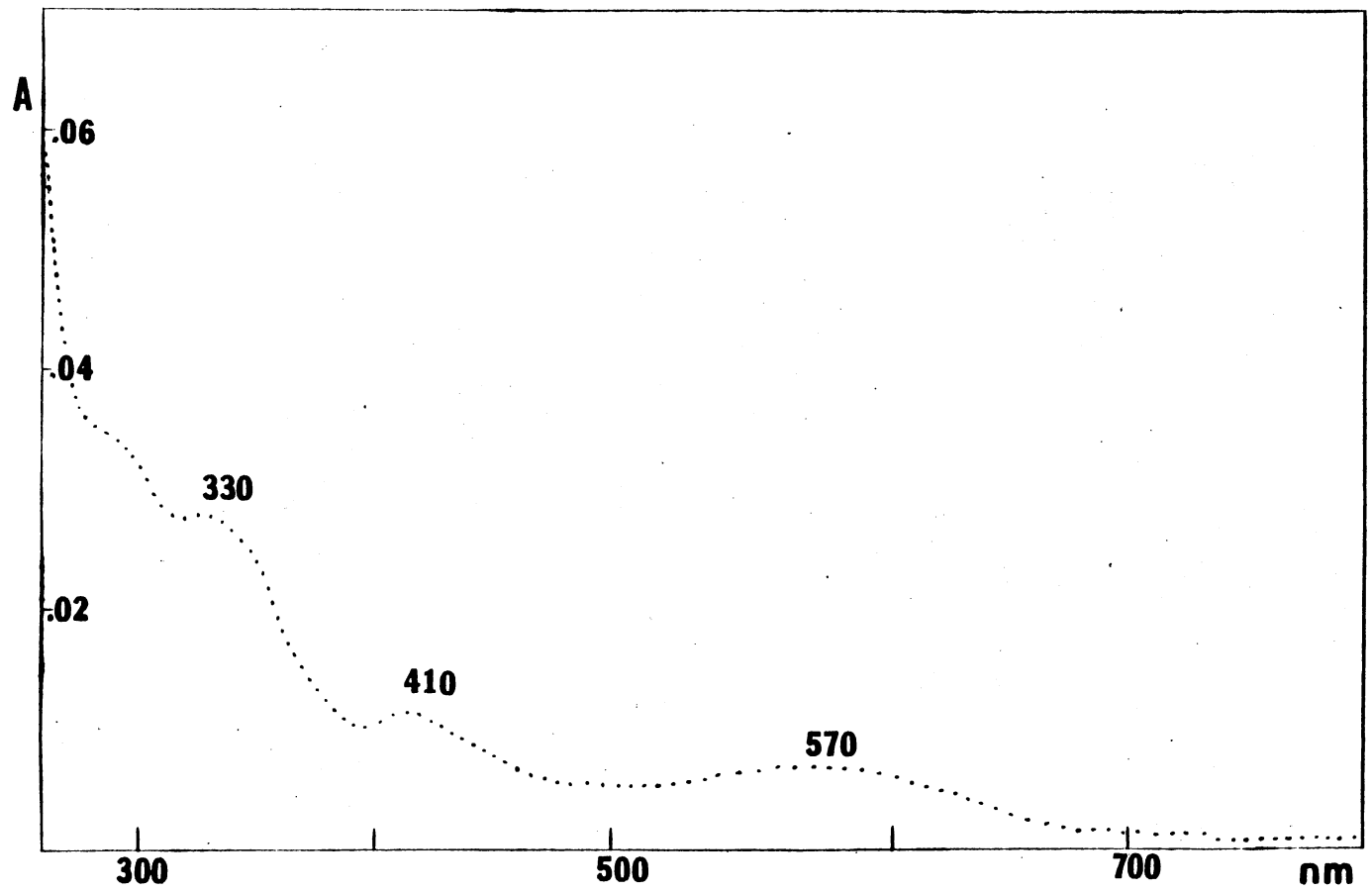


Figure 35. UV-visible Spectrum of the Chloroform Extract of the Solution Containing Morphine Sulfate and Concentrated Sulfuric Acid

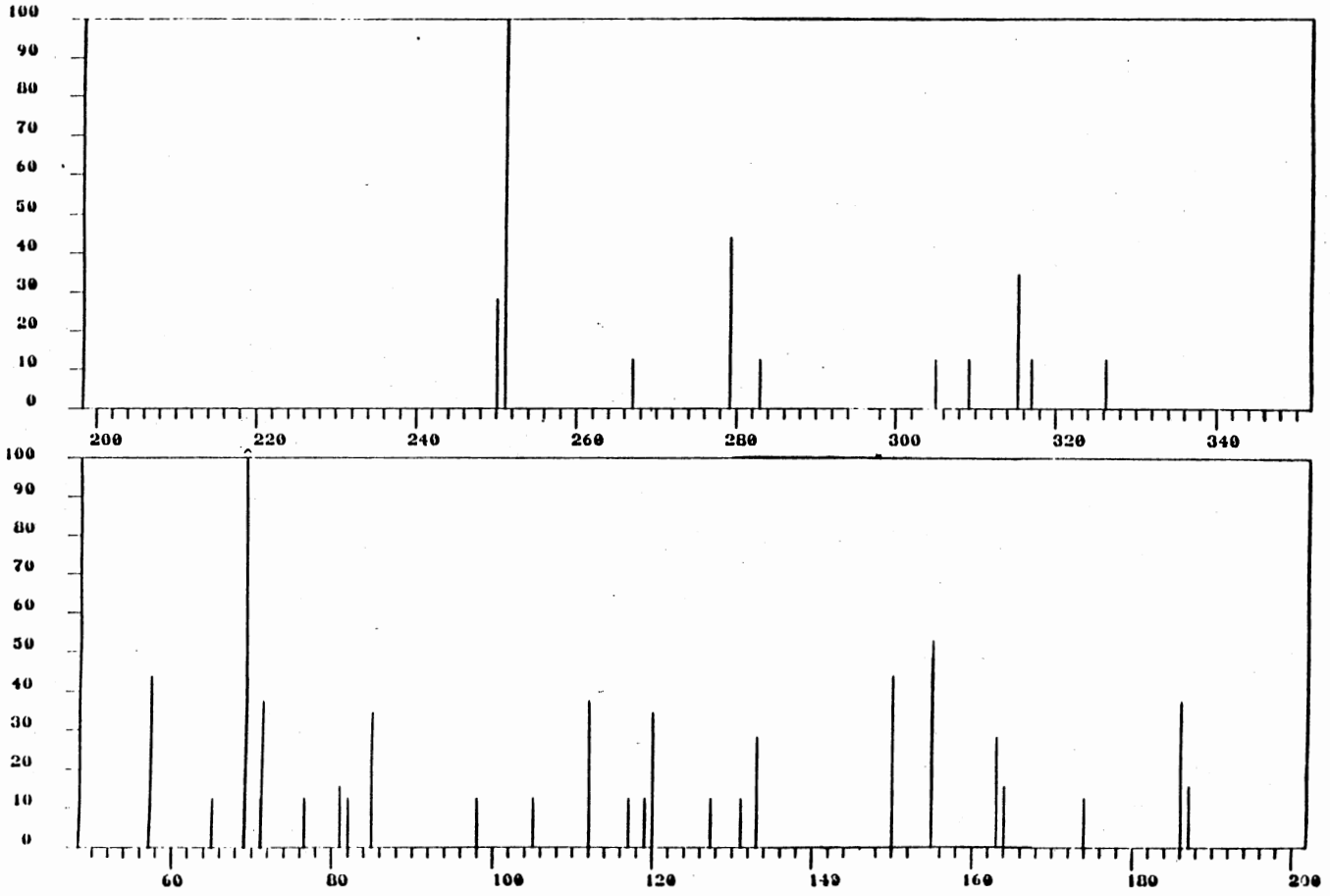


Figure 36. Mass Spectrum of the Chloroform Extracted Solution from Morphine Sulfate-Froehde Reaction

Apomorphine Hydrochloride

Like morphine sulfate, a solution of apomorphine hydrochloride in concentrated sulfuric acid undergoes a series of color changes with time (Table IX) with accompanying changes in the UV-visible and CD spectra.

TABLE IX

COLOR CHANGE DATA OF APOMORPHINE IN CONCENTRATED SULFURIC ACID

Time Interval	Color Observed
0	clear
2 days	purple-gray
15 days	brownish-pink

The UV spectrum (Figure 37) of a freshly prepared solution in concentrated sulfuric acid is quite different from that of the solution in distilled water (Figure 38). In the acid solution, the principal bands with maxima around 240 and 280 nm are shifted to longer wavelengths and the relative intensities again changed with time showing a decrease at 240 nm and an increase at 280 nm (Figures 39, 40). Unlike morphine sulphate, the CD

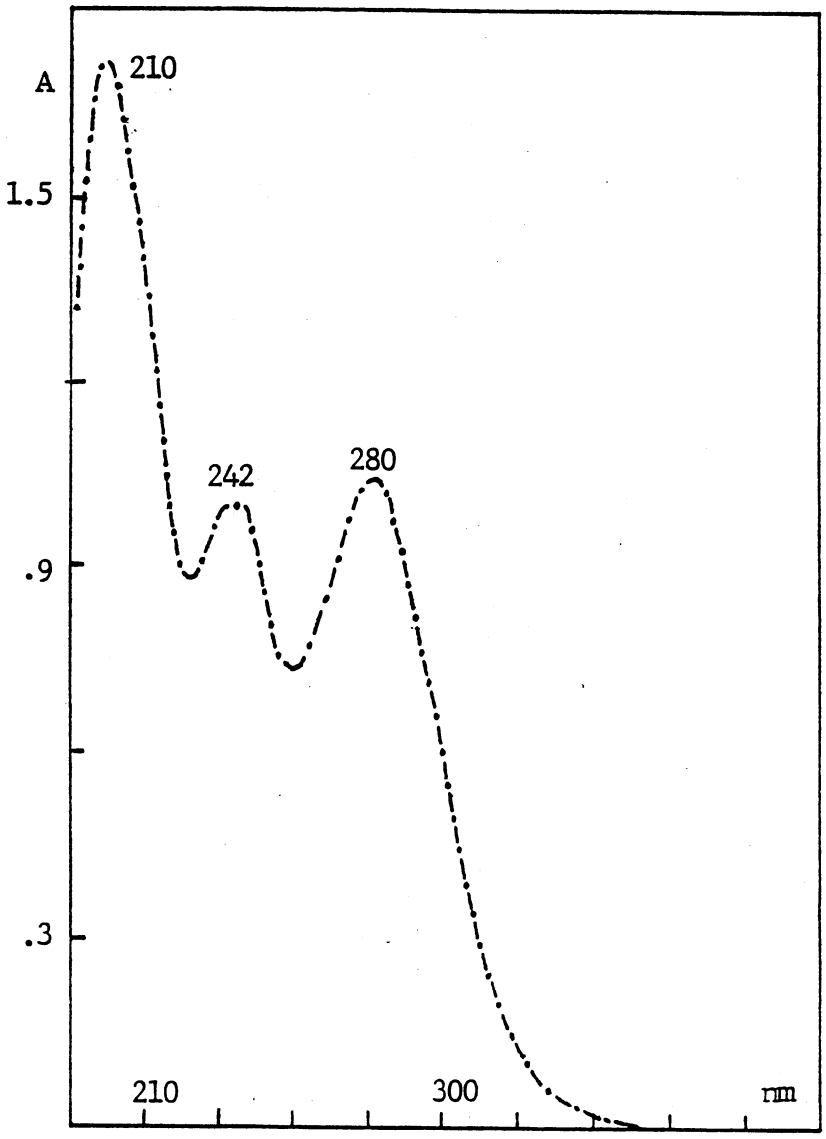


Figure 37. UV Spectrum of Apomorphine Hydrochloride in Concentrated Sulfuric Acid (After Mixing)

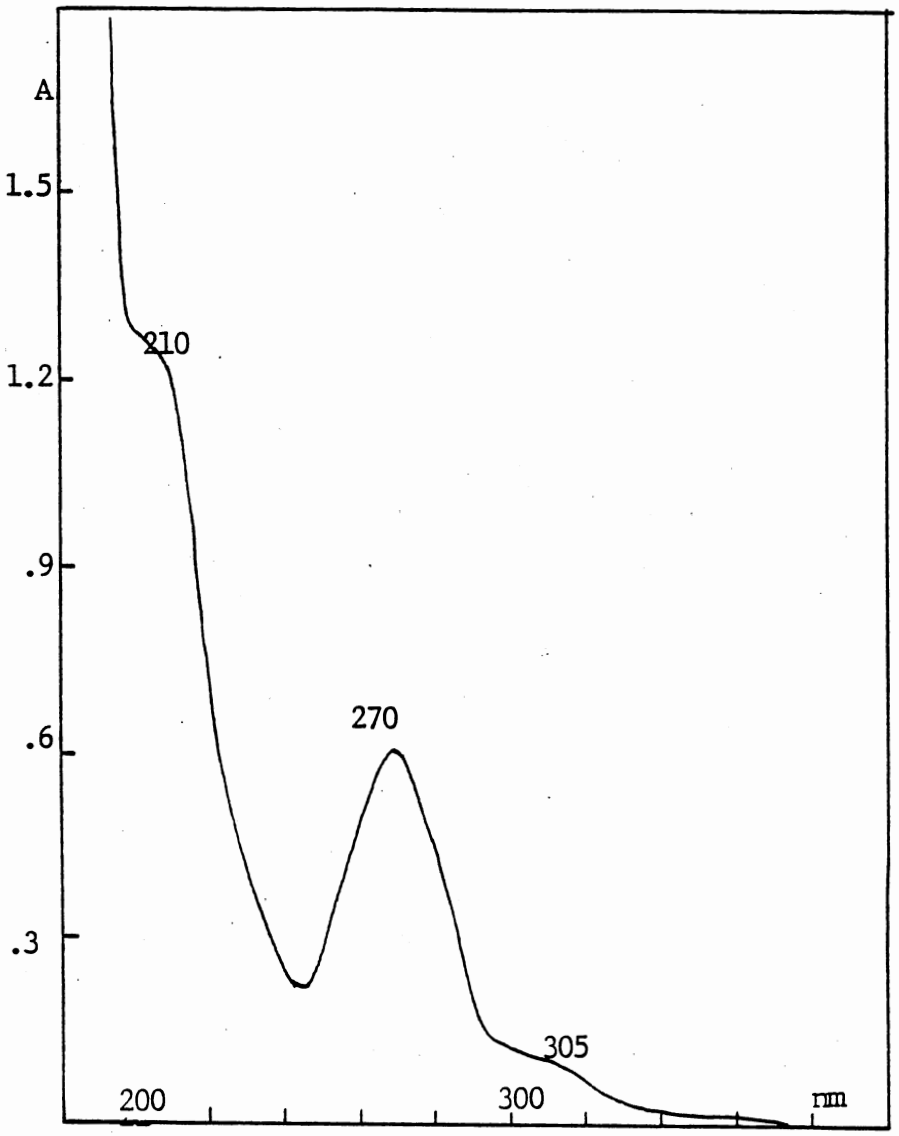


Figure 38. UV Spectrum of Apomorphine Hydrochloride in Distilled Water

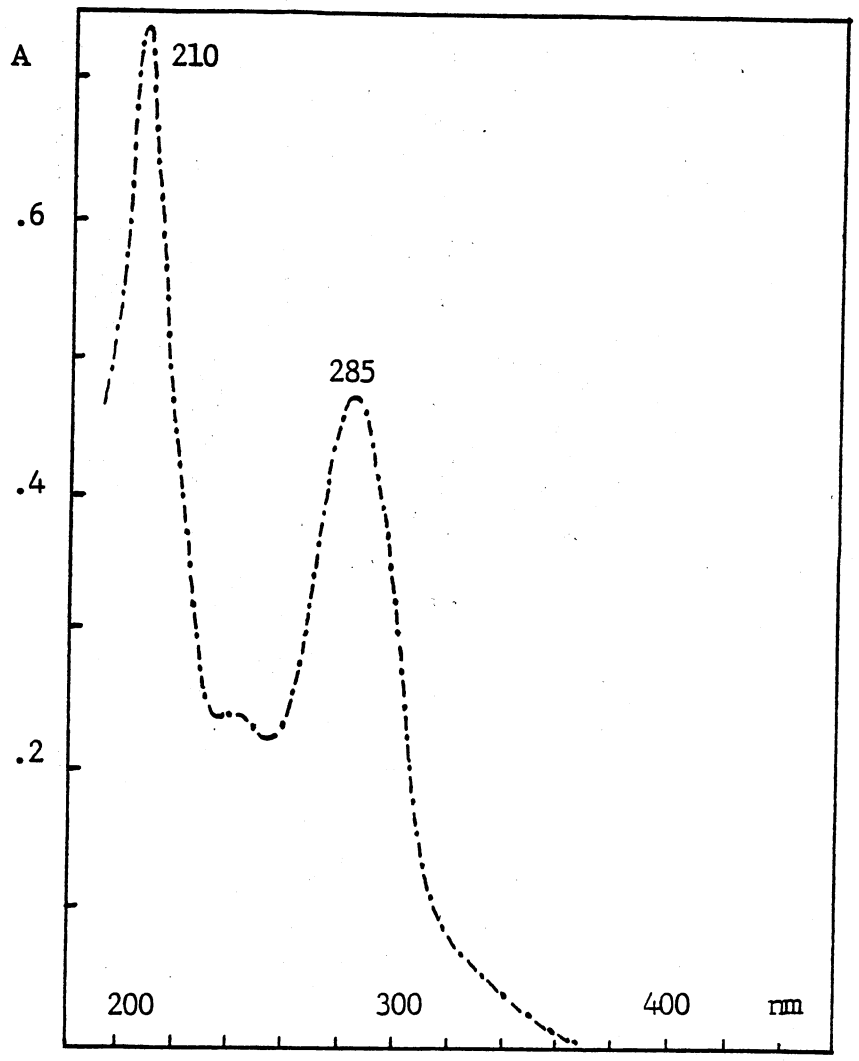


Figure 39. UV Spectrum of Apomorphine Hydrochloride in Concentrated Sulfuric Acid After 2 Weeks

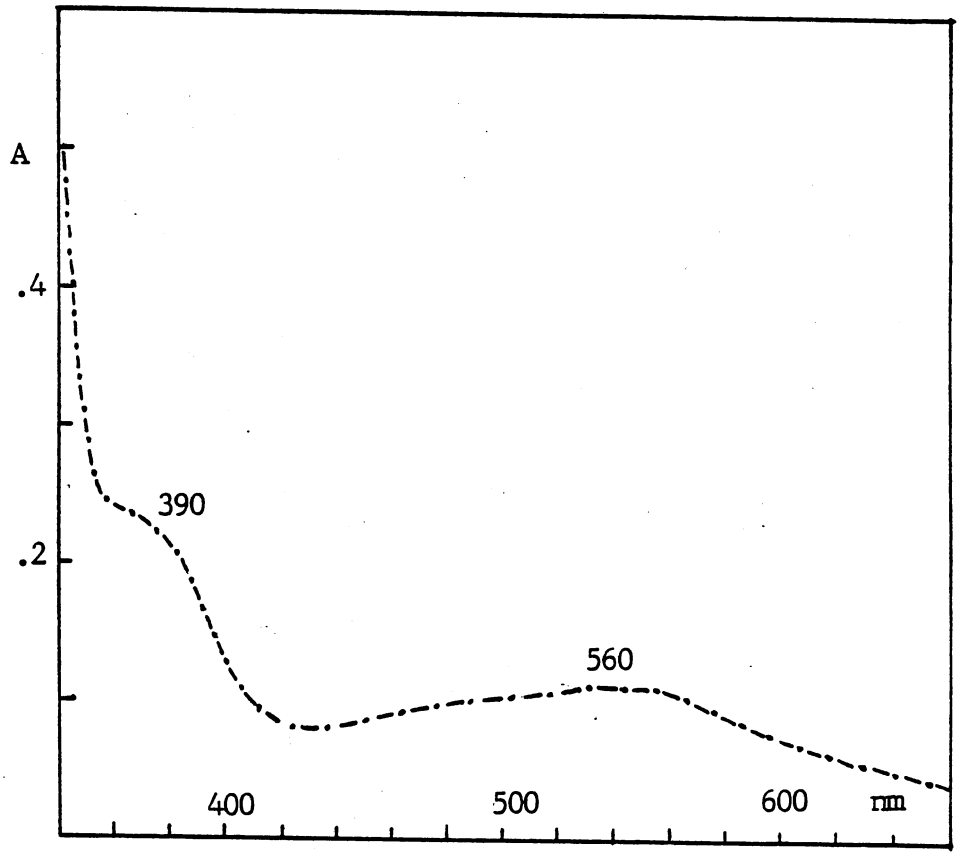


Figure 40. Visible Spectrum of Apomorphine Hydrochloride in Concentrated Sulfuric Acid After 2 Weeks

spectrum (Figure 41) of apomorphine hydrochloride in concentrated sulfuric acid is not inverted when compared to the spectrum in aqueous solution and has characteristic wavelengths λ^{+}_{max}, λ^{-}_{max} and λ^{o} only slightly removed from those for apomorphine hydrochloride in distilled water (Figure 42). On dilution of the acid solution with water the spectrum changes to become essentially that for the aqueous solution. This indicates the presence of a reversible reaction. The air oxidation of apomorphine hydrochloride in concentrated sulfuric acid occurs gradually with time. The general appearance of the CD spectrum of apomorphine resembles that for morphine. Characteristic wavelengths differ by only a few nanometers: λ^{+}_{max} = 285 nm, λ^{o} = 257 nm and λ^{-}_{max} = 232 nm. Using the Froehde reagent the reaction occurred much more quickly. A dark purple color developed within an hour. After the solution was allowed to stand in air at room temperature for two days, it was extracted with chloroform. A purple color developed in the chloroform layer. The UV-visible spectrum (Figure 43) of this solution is identical to that for the corresponding morphine oxidation product extract in chloroform.

The apomorphine hydrochloride reaction with concentrated sulfuric acid alone was extracted in the same manner after it stood at room temperature, in air, for two weeks. The chloroform extract was clear in color. At the highest instrument sensitivity, however, the

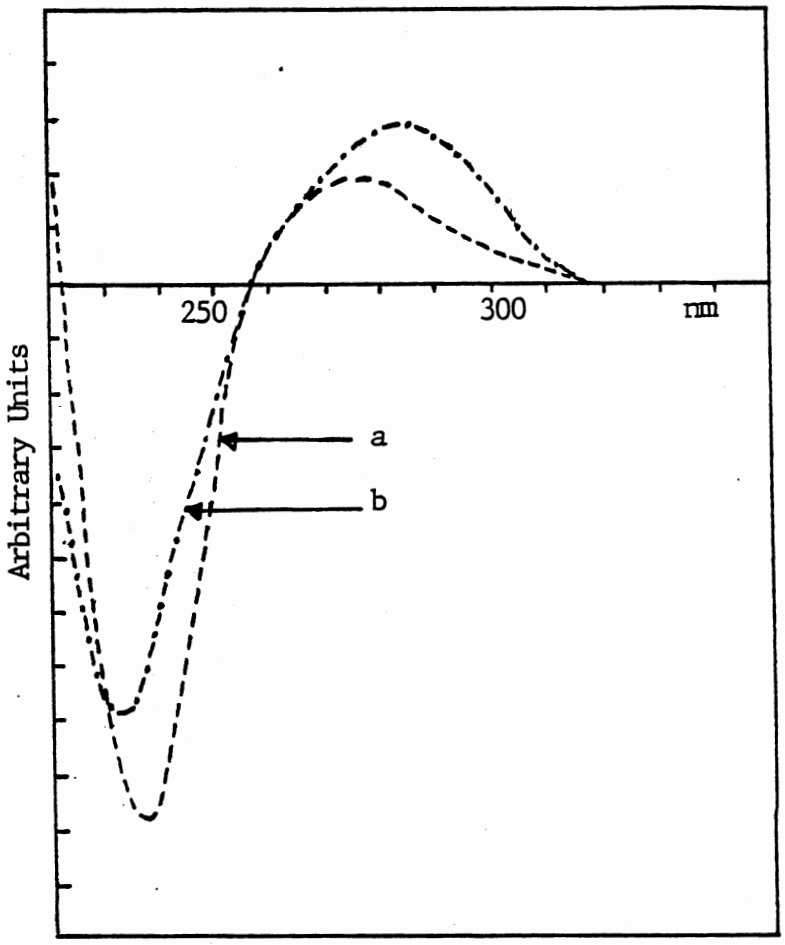


Figure 41. CD Spectra of Apomorphine Hydrochloride in Concentrated Sulfuric Acid. a) After Mixing, b) After Standing at Room Temperature for 2 Weeks

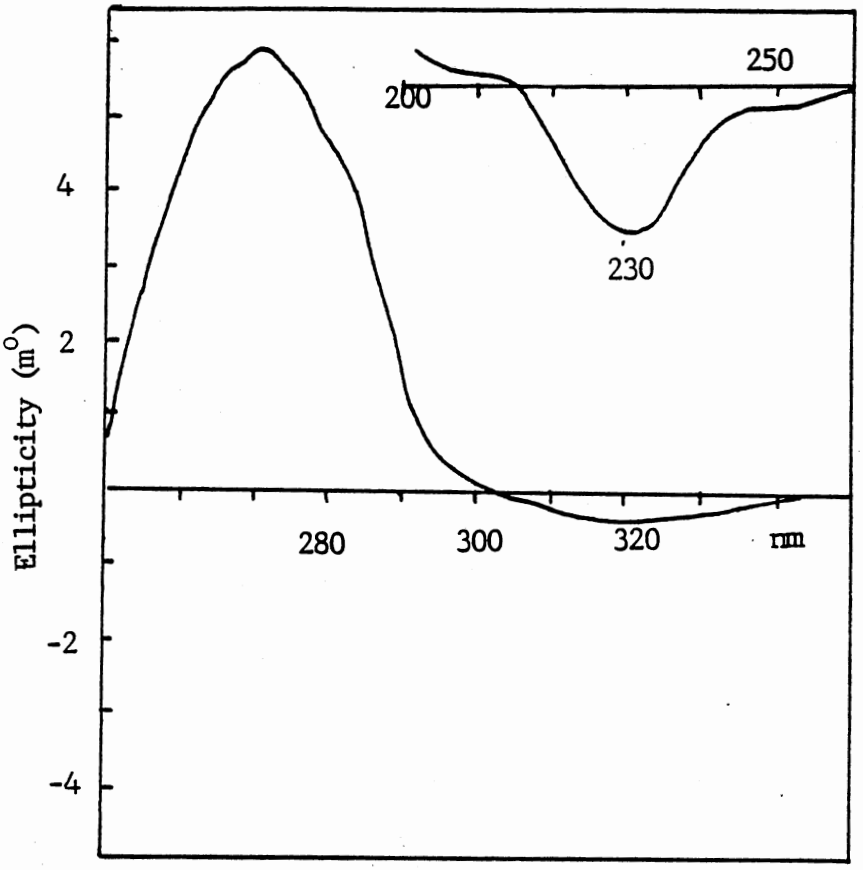


Figure 42. CD Spectra of Apomorphine Hydrochloride in Distilled Water

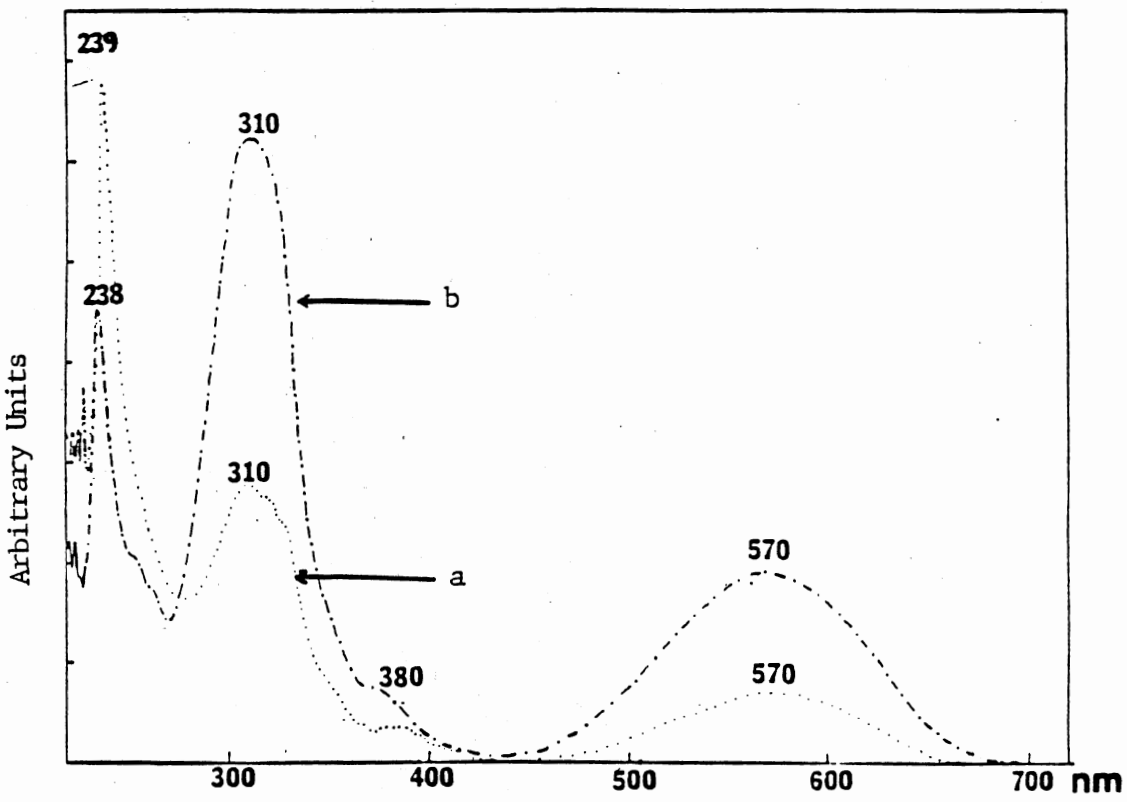


Figure 43. UV-visible Spectra of the Chloroform Extracts of a) Apomorphine Hydrochloride with Concentrated Sulfuric Acid, b) with Froehde Reagent

UV-visible spectrum (Figure 43) obtained is similar to that for the extract of the apomorphine oxidation product after reaction with Froehde reagent. Relative band intensities are not exactly comparable, which may be attributed to different distributions of the products of the reactions. That mixtures are obtained is evident from the TLC study described in the next section.

Thin-layer Chromatography

The purple chloroform extracts from the final solutions of the morphine sulfate-color test reagents and apomorphine hydrochloride-Froehde reactions were spotted for a TLC separation. Under the conditions used, the mixture separated into three components with Rf values equal to .34, .72 and .90, respectively. The slowest advancing component was green in color. The other two components were only observable under UV light. TLC comparisons were run against morphine and apomorphine, under the same conditions. Only one spot was observed for morphine, a colorless, UV sensitive component with an Rf value equal to 0.39 and also only one green and UV active spot for apomorphine (Rf = 0.73).

X-ray Structural Analysis

Structural Comparison of Morphine Sulfate and Morphine Methyliodide

Recrystallized morphine sulfate and morphine methyliodide were obtained as transparent, colorless single

crystals. Photographic investigations indicated orthorhombic symmetry for both structures. Systematic absences are compatible with space groups $P22_12_1$ and $P2_12_12_1$, respectively. The calculated unit cell dimensions are tabulated in Tables X and XI. Data were collected for a total of 4278 points for morphine sulfate and 3001 points for morphine methyliodide. After the removal of redundant and space group-forbidden data, 1754 and 2575 "legitimate" reflections were considered valid ($I > 3.00\sigma(I)$) for morphine sulfate and morphine methyliodide, respectively (Appendix A and B).

The final atomic positional and thermal parameters; together with their standard deviations are presented in Tables XII, XIII, XIV, XV, XVI, XVII and XVIII. The least squares refinement produced the final R factor for morphine sulfate equal to 6.2% and 6.1% for morphine methyliodide. The bond angles and bond distances between atoms in these two molecules are listed in Tables XIX and XX.

The confirmations of ring D and ring E of the two morphine salts were compared with those for morphine hydrate. The torsional angles of ring D and ring E of morphine hydrate were calculated based on the structural information reported by Bye (46) and are listed in Table XXI.

Three dimensional ORTEP projections are presented in Figures 44 and 45, respectively. The packing diagram showing the hydrogen bonding network of morphine sulfate,

TABLE X

CRYSTAL DATA FOR $(C_{17}H_{20}NO_3^+)_2SO_4^= \cdot 3H_2O$

Formula	$C_{34}H_{38}N_2O_6 \cdot H_2SO_4 \cdot 3H_2O$
MWT	722.81
a	8.463(3)A^o
b	6.825(2)
c	30.71(1)
$\alpha = \beta = \gamma$	90.0°
V	1774(1)A^{o3}
F(000)	708
λMok_α	0.71069A^o
μ_{MoK_α}	1.6477
D_{calc}	1.3529 g cm^{-1}
Z	2
Space	$P22_12_1$
Systematic absences	001, $1 \neq 2n$
	0k0, $k \neq 2n$
Obs. reflections	1754
Final R Factor	6.2%

TABLE XI

CRYSTAL DATA FOR $(C_{18}H_{22}NO_3)^+I^- \cdot H_2O$

Formula	$C_{18}H_{22}NO_3I \cdot H_2O$
MST	445.298
a	9.574(1)A^o
b	10.614(2)
c	17.549(4)
$\alpha = \beta = \gamma$	90.0^o
V	1783.3(6)A^{o3}
F(000)	856
λMok_α	0.7169A
μ_{MoK_α}	77.7342
D_{calc}	1.6582 g cm^{-1}
Z	4
Space group	$P2_12_12_1$
Systematic absences	h00, h ≠ 2n
	0k0, k ≠ 2n
	001, 1 ≠ 2n
Obs. reflections	2575
Final R factor	6.1%

TABLE XII

NONHYDROGEN POSITIONAL PARAMETERS FOR $(C_{17}H_{20}NO_3^+)_2SO_4^=$

Atom	x(σ(x))	y(σ(y))	z(σ(z))
S1	0.6527(3)	0.5000	0.5000
01	0.4294(7)	0.1037(11)	0.2791(2)
02	0.3741(7)	0.6331(9)	0.3823(2)
03	0.3315(6)	0.2453(9)	0.3623(2)
0111	0.7539(7)	0.3284(9)	0.4926(2)
0112	0.5537(8)	0.4730(11)	0.5380(2)
0113	0.5251(8)	0.5064(15)	0.3038(2)
0114	0.6911(8)	0.3011(10)	0.0108(2)
0115	0.9093(10)	0.0000(0)	0.0000(0)
N1	-.2470(7)	0.1135(9)	0.4185(2)
C1	-.0034(10)	0.0153(14)	0.2802(3)
C2	0.1561(10)	0.0129(14)	0.2669(3)
C3	0.2760(10)	0.0841(12)	0.2930(3)
C4	0.2333(9)	0.1507(11)	0.3332(3)
C5	0.2319(9)	0.3281(10)	0.3976(3)
C6	0.2207(11)	0.5536(11)	0.3900(3)
C7	0.1052(11)	0.6083(11)	0.3561(3)
C8	-.0372(10)	0.5260(10)	0.3567(3)
C9	-.2213(8)	0.2444(11)	0.3790(3)
C10	-.2102(8)	0.1260(13)	0.3366(3)
C11	-.0434(8)	0.0858(10)	0.3216(3)
C12	0.0791(8)	0.1382(10)	0.3484(3)
C13	0.0672(8)	0.2301(10)	0.3930(3)
C14	-.0746(8)	0.3714(9)	0.3900(3)
C15	0.0405(8)	0.0828(10)	0.4299(3)
C16	-.1114(9)	-.0283(10)	0.4252(3)
C17	-.4023(10)	0.0080(21)	0.4195(5)

TABLE XIII

HYDROGEN POSITIONAL PARAMETERS FOR $(C_{17}H_{20}NO_3^+)_2SO_4^=$

Atom	x(σ(x))	y(σ(y))	z(σ(z))
HC1	-.079(10)	0.003(17)	0.256(28)
HC2	0.192(7)	-.016(11)	0.238(2)
HC5	0.307(12)	0.293(15)	0.422(3)
HC6	0.186(8)	0.610(10)	0.419(3)
HC7	0.155(6)	0.695(8)	0.338(2)
HC8	-.126(7)	0.563(8)	0.335(2)
HC9	-.322(9)	0.309(11)	0.376(2)
H1C10	-.299(13)	0.034(17)	0.331(3)
H2C10	-.274(12)	0.217(16)	0.316(3)
HC14	-.104(6)	0.424(7)	0.416(2)
H1C15	0.112(6)	0.004(9)	0.431(2)
H2C15	0.039(10)	0.153(13)	0.457(3)
H1C16	-.127(8)	-.086(9)	0.444(2)
H2C16	-.118(9)	-.107(12)	0.399(3)
H1C17	-.456(17)	0.118(21)	0.419(5)
H2C17	-.446(19)	-.077(22)	0.440(5)
H3C17	-.422(13)	-.098(17)	0.395(3)
HO1	0.489(15)	0.240(22)	0.294(4)
HO2	0.440(26)	0.706(34)	0.403(7)
HN1	-.250(7)	0.166(9)	0.450(2)

TABLE XIV

NONHYDROGEN ATOM ANISOTROPIC THERMAL PARAMETERS FOR $(C_{17}H_{20}NO_3^+)_2SO_4^=$

Atom	10^3U_{11}	10^3U_{22}	10^3U_{33}	10^3U_{12}	10^3U_{13}	10^3U_{23}
S1	31(1)	30(1)	47(2)	0(0)	0(0)	-2(1)
O1	39(3)	89(5)	63(5)	2(4)	15(3)	-15(4)
O2	75(4)	63(4)	42(5)	-39(4)	9(4)	3(3)
O3	35(3)	62(4)	21(4)	-9(3)	2(2)	-16(3)
O111	84(4)	62(3)	28(5)	36(4)	3(4)	-3(3)
O112	73(4)	80(5)	63(6)	-4(4)	-46(4)	11(4)
O113	71(4)	120(4)	67(6)	6(6)	25(4)	39(5)
O114	77(4)	78(4)	59(6)	-28(4)	3(4)	-13(4)
O115	48(4)	130(9)	53(8)	0(0)	0(0)	27(8)
N1	33(3)	34(3)	27(5)	-4(3)	3(3)	0(3)
C1	61(5)	45(4)	13(6)	-2(4)	-6(4)	-3(4)
C2	63(5)	46(4)	26(7)	0(5)	18(5)	-23(4)
C3	50(4)	43(4)	28(7)	9(4)	3(4)	-3(4)
C4	42(4)	40(4)	25(6)	3(3)	-5(4)	-5(4)
C5	38(4)	34(3)	40(7)	-6(3)	-2(4)	-2(4)
C6	63(5)	38(4)	18(8)	-17(4)	15(5)	-9(4)
C7	61(5)	28(3)	42(8)	-9(3)	17(5)	7(4)
C8	59(5)	30(5)	17(7)	11(3)	3(4)	3(3)
C9	35(3)	34(3)	36(7)	5(3)	0(4)	2(4)
C10	36(4)	48(4)	46(8)	-7(4)	-10(4)	3(5)
C11	43(4)	34(3)	8(6)	-3(3)	-7(4)	1(4)
C12	38(3)	24(3)	32(7)	0(3)	-3(4)	1(3)
C13	33(3)	27(3)	28(6)	2(3)	-3(3)	-2(3)
C14	39(3)	26(3)	35(6)	5(3)	8(4)	-9(3)
C15	32(3)	26(3)	49(7)	2(3)	-3(4)	8(4)
C16	46(4)	26(3)	40(7)	-1(3)	-1(4)	6(4)
C17	36(4)	66(6)	94(11)	-18(5)	7(5)	5(7)

TABLE XIV (Continued)

$$\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*]$$

TABLE XV

HYDROGEN ISOTROPIC THERMAL PARAMETERS FOR $(C_{17}H_{20}NO_3^+)_2SO_4^=$

Atom	10^2U	Atom	10^2U
HC1	10(3)	HC2	3(2)
HC5	7(3)	HC6	3(2)
HC7	0(1)	HC8	1(2)
HC9	5(2)	H1C10	11(4)
H2C10	8(4)	HC14	0(1)
H1C15	2(2)	H2C15	8(3)
H1C16	2(2)	H2C16	4(2)
H1C17	13(6)	H2C17	14(7)
H3C17	14(4)	H01	16(6)
H02	47(13)	HN1	2(2)

TABLE XVI

NONHYDROGEN POSITIONAL PARAMETERS FOR $(C_{18}H_{22}NO_3)^+I^-$

Atom	x(σ(x))	y(σ(y))	z(σ(z))
I1	-.0021(1)	0.0475(1)	-.1033(0)
N1	-.0120(10)	0.4205(6)	0.0414(4)
01	-.1314(11)	0.3350(9)	0.4342(4)
02	0.3102(11)	0.2273(9)	0.3486(4)
03	0.1016(8)	0.3857(7)	0.3325(4)
04	-.3310(12)	0.2172(9)	0.5114(5)
C1	-.2678(11)	0.2522(12)	0.2412(7)
C2	-.2637(11)	0.2782(11)	0.3211(6)
C3	-.1433(12)	0.3208(10)	0.3556(6)
C4	-.0291(9)	0.3492(8)	0.3106(6)
C5	0.1954(10)	0.3723(9)	0.2663(6)
C6	0.2831(12)	0.2557(12)	0.2695(8)
C7	0.2227(11)	0.1417(9)	0.2280(6)
C8	0.1537(11)	0.1540(9)	0.1634(6)
C9	0.0017(15)	0.2870(7)	0.0766(4)
C10	-.1358(11)	0.2423(10)	0.1145(6)
C11	-.1504(10)	0.2816(9)	0.1972(6)
C12	-.0382(9)	0.3343(8)	0.2322(5)
C13	0.0948(9)	0.3757(8)	0.1962(5)
C14	0.1275(10)	0.2845(8)	0.1305(6)
C15	0.0822(10)	0.5093(9)	0.1618(6)
C16	-.0314(10)	0.5140(8)	0.1042(6)
C17	-.1335(14)	0.4272(14)	-.0129(8)
C18	0.1151(12)	0.4487(14)	-.0061(7)

TABLE XVII

NONHYDROGEN ATOM ANISOTROPIC THERMAL PARAMETERS FOR $(C_{18}H_{22}NO_3)^+I^-$

Atom	10^3U_{11}	10^3U_{22}	10^3U_{33}	10^3U_{12}	10^3U_{13}	10^3U_{23}
I1	37(0)	40(0)	42(0)	5(0)	-1(0)	-3(0)
N1	30(4)	23(3)	28(4)	4(3)	2(4)	1(2)
O1	80(6)	49(4)	18(4)	-5(5)	11(4)	-4(3)
O2	88(7)	53(5)	26(5)	26(5)	-8(4)	9(4)
O3	38(4)	32(4)	20(4)	-1(3)	-1(3)	-4(3)
O4	85(7)	64(6)	34(5)	-16(6)	14(5)	6(4)
C1	25(5)	39(6)	39(8)	-2(4)	0(4)	-1(5)
C2	33(5)	38(6)	29(7)	3(4)	10(4)	12(5)
C3	40(6)	26(5)	28(6)	10(4)	3(4)	2(4)
C4	35(5)	19(4)	24(5)	1(3)	0(3)	0(3)
C5	28(4)	27(4)	27(6)	-6(3)	-3(4)	3(4)
C6	30(5)	38(6)	31(6)	6(4)	-3(4)	5(5)
C7	43(5)	22(5)	39(6)	11(4)	11(5)	11(4)
C8	43(5)	15(4)	36(6)	5(4)	3(4)	-2(4)
C9	39(4)	17(3)	23(4)	5(5)	5(5)	-5(3)
C10	39(5)	26(5)	32(6)	-7(4)	-1(4)	-1(4)
C11	29(4)	22(4)	27(6)	-1(3)	-1(4)	0(3)
C12	27(4)	18(4)	24(5)	1(3)	2(3)	-3(3)
C13	23(4)	17(4)	26(5)	-7(3)	-3(3)	-5(3)
C14	27(4)	10(4)	33(6)	0(3)	1(4)	0(3)
C15	34(4)	19(4)	35(6)	3(3)	-4(4)	9(4)
C16	45(6)	28(4)	19(5)	16(3)	0(4)	2(4)
C17	52(7)	54(9)	29(7)	3(6)	-15(6)	7(6)
C18	34(5)	37(6)	44(7)	2(5)	2(5)	-2(6)

$$\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*]$$

TABLE XVIII

HYDROGEN POSITIONAL PARAMETERS FOR $(C_{18}H_{22}NO_3)^+I^-$

Atom	x	y	z
HC1	-.3511	0.2149	0.2171
HC2	-.3443	0.2633	0.3482
HC5	0.2511	0.4718	0.2722
HC6	0.3737	0.2741	0.2462
HC7	0.2528	0.0588	0.2473
HC8	0.1202	0.0788	0.1374
HC9	0.0000	0.2361	0.0286
H1C10	-.1400	0.1504	0.1115
H2C10	-.2055	0.3199	0.1031
HC14	0.2141	0.3046	0.1148
H1C15	0.0719	0.5718	0.2025
H2C15	0.1771	0.5134	0.1540
H1C16	-.0385	0.5969	0.0795
H2C16	-.1175	0.5142	0.1011
H1C17	0.1061	0.5365	-.0239
H2C17	0.1126	0.3947	0.0518
H3C17	0.1979	0.4429	0.0104
H1C18	-.1223	0.4950	-.0500
H2C18	-.1428	0.3474	-.0432
H3C18	-.2420	0.4418	0.0184
HO1	-.2154	0.3018	0.4819
HO2	0.3333	0.1420	0.3666

TABLE XIX

BOND LENGTHS(A°) AND ANGLES(°) FOR $(C_{17}H_{20}NO_3^+)_2SO_4^=$

S1-0111	1.468(6)	S1-0112	1.448(7)
S1-0111'	1.468(6)	S1-0112'	1.448(7)
0111-S1-0111'	108.7(4)	0111'-S1-0112	109.3(4)
0111-S1-0112	111.1(4)	0111'-S1-0112'	111.1(4)
0111-S1-0112'	108.4(4)	0112-S1-0112'	109.3(4)
C1-C2	1.41(1)	C1-C11	1.40(1)
C2-3	1.38(1)	C3-01	1.37(1)
C3-C4	1.36(1)	C4-C12	1.39(1)
C4-03	1.38(1)	C5-03	1.48(1)
C5-C6	1.56(1)	C5-C13	1.55(1)
C6-02	1.43(1)	C6-C7	1.48(1)
C7-C8	1.33(1)	C8-C14	1.50(1)
C9-C10	1.54(1)	C9-C14	1.55(1)
C10-C11	1.51(1)	C11-C12	1.37(1)
C12-C13	1.51(1)	C13-C14	1.54(1)
C13-C15	1.53(1)	C15-C16	1.50(1)
N1-C9	1.52(1)	N1-C16	1.52(1)
N1-C17	1.50(1)		
C1-C2-C3	121.9(8)	C2-C3-C4	116.6(8)
C2-C3-01	123.1(8)	01-C3-C4	120.1(8)
C3-C4-03	125.6(7)	C3-C4-C12	122.2(7)
C12-C4-03	112.2(7)	C11-C12-C4	121.7(8)
C13-C12-C4	110.0(6)	C11-C12-C13	127.0(6)
C10-C11-C12	118.4(7)	C1-C11-C12	116.8(7)
C1-C11-C10	124.5(7)	C11-C1-C2	120.0(8)
C4-03-C5	108.0(6)	03-C5-C6	107.6(7)
C13-C5-03	106.3(6)	C13-C5-C6	110.9(6)
C5-C13-C12	101.6(6)	C6-C13-C14	115.8(6)
C5-C13-C15	110.3(6)	C12-C13-C14	104.9(6)
C12-C13-C15	114.1(6)	C14-C13-C15	109.9(6)
C5-C6-C7	113.3(7)	C5-C6-02	110.2(6)

TABLE XIX (Continued)

O2-C6-C7	112.8(7)	C6-C7-C8	118.9(8)
C7-C8-C14	119.8(7)	C8-C14-C13	108.4(6)
C8-C14-C9	114.4(7)	C13-C14-C9	106.7(5)
C9-C10-C11	114.4(6)	C10-C9-C14	115.4(6)
N1-C9-C10	112.0(6)	N1-C9-C14	105.6(6)
C13-C15-C16	112.7(7)	C15-C16-N1	109.8(5)
C16-N1-C9	112.0(6)	C17-N1-C9	115.1(8)
C17-N1-C16	110.7(7)		

TABLE XX

BOND LENGTHS(A°) AND ANGLES(°) FOR $(C_{18}H_{22}NO_3)^+I^-$

C1-C2	1.43(2)	C1-C11	1.40(2)
C2-C3	1.38(2)	C3-O1	1.40(2)
C3-C4	1.38(2)	C4-C12	1.39(1)
C4-O3	1.36(1)	C5-O3	1.48(1)
C5-C6	1.50(2)	C5-C13	1.56(1)
C6-O2	1.44(2)	C6-C7	1.53(2)
C7-C8	1.32(2)	C8-C14	1.52(1)
C9-C10	1.55(2)	C9-C14	1.53(2)
C10-C11	1.52(2)	C11-C12	1.36(1)
C12-C13	1.49(1)	C13-C14	1.54(1)
C13-C15	1.54(1)	C15-C16	1.49(1)
N1-C9	1.55(1)	N1-C16	1.50(1)
N1-C17	1.50(2)	N1-C18	1.50(2)

C1-C2-C3	121(1)	C2-C3-C4	119(1)
C2-C3-O1	123(1)	O1-C3-C4	119(1)
C3-C4-O3	129(1)	C3-C4-C12	120(1)
C12-C4-O3	112(1)	C11-C12-C4	123(1)
C13-C12-C4	109(1)	C11-C12-C13	127(1)
C10-C11-C12	118(1)	C1-C11-C12	118(1)
C1-C11-C10	123(1)	C11-C1-C2	118(1)
C4-O3-C5	108(1)	O3-C5-C6	113(1)
C13-C5-O3	104(1)	C13-C5-C6	113(1)
C5-C13-C12	101(1)	C5-C13-C14	117(1)
C5-C13-C15	112(1)	C12-C13-C14	108(1)
C12-C13-C15	111(1)	C14-C13-C15	107(1)
C5-C6-C7	115(1)	C5-C6-O2	108(1)
O2-C6-C7	111(1)	C6-C7-C8	121(1)
C7-C8-C14	120(1)	C8-C14-C13	109(1)
C8-C14-C9	112(1)	C13-C14-C9	107(1)
C9-C10-C11	114(1)	C10-C9-C14	113(1)
N1-C9-C10	112(1)	N1-C9-C14	109(1)

TABLE XX (Continued)

C13-C15-C16	111(1)	C15-C16-N1	113(1)
C16-N1-C9	109(1)	C17-N1-C9	110(1)
C17-N1-C16	112(1)	C17-N1-C18	105(1)
C18-N1-C9	111(1)	C18-N1-C16	110(1)

TABLE XXI

TORSIONAL ANGLES OF MORPHINE AND MORPHINE SALTS

Dihedral Angle	Morphine methyl-iodide·H_2O	Morphine sulfate·$3H_2O$	Morphine·H_2O
C5-C6-C7-C8	37.0(16)	46.3(11)	41.5(6)
C6-C7-C8-C14	-2.6(16)	-3.6(12)	-4.9(6)
C7-C8-C14-C13	-38.7(13)	-43.4(10)	-39.0(5)
C8-C14-C13-C5	48.0(10)	48.3(10)	46.9(5)
C14-C13-C5-C6	-17.1(12)	-9.9(11)	-13.1(5)
C13-C5-C6-C7	-24.2(13)	-36.4(10)	-29.2(5)
C15-C13-C14-C9	121.0(9)	122.2(8)	123.4(4)
C13-C14-C9-N1	64.5(9)	65.5(8)	65.0(4)
C14-C9-N1-C16	-59.8(11)	-64.8(7)	-62.5(5)
C9-N1-C16-C15	56.0(11)	57.4(8)	53.3(6)
N1-C16-C15-C13	-57.1(10)	-51.5(9)	-46.2(5)
C16-C15-C13-C14	60.1(10)	55.6(8)	54.1(5)

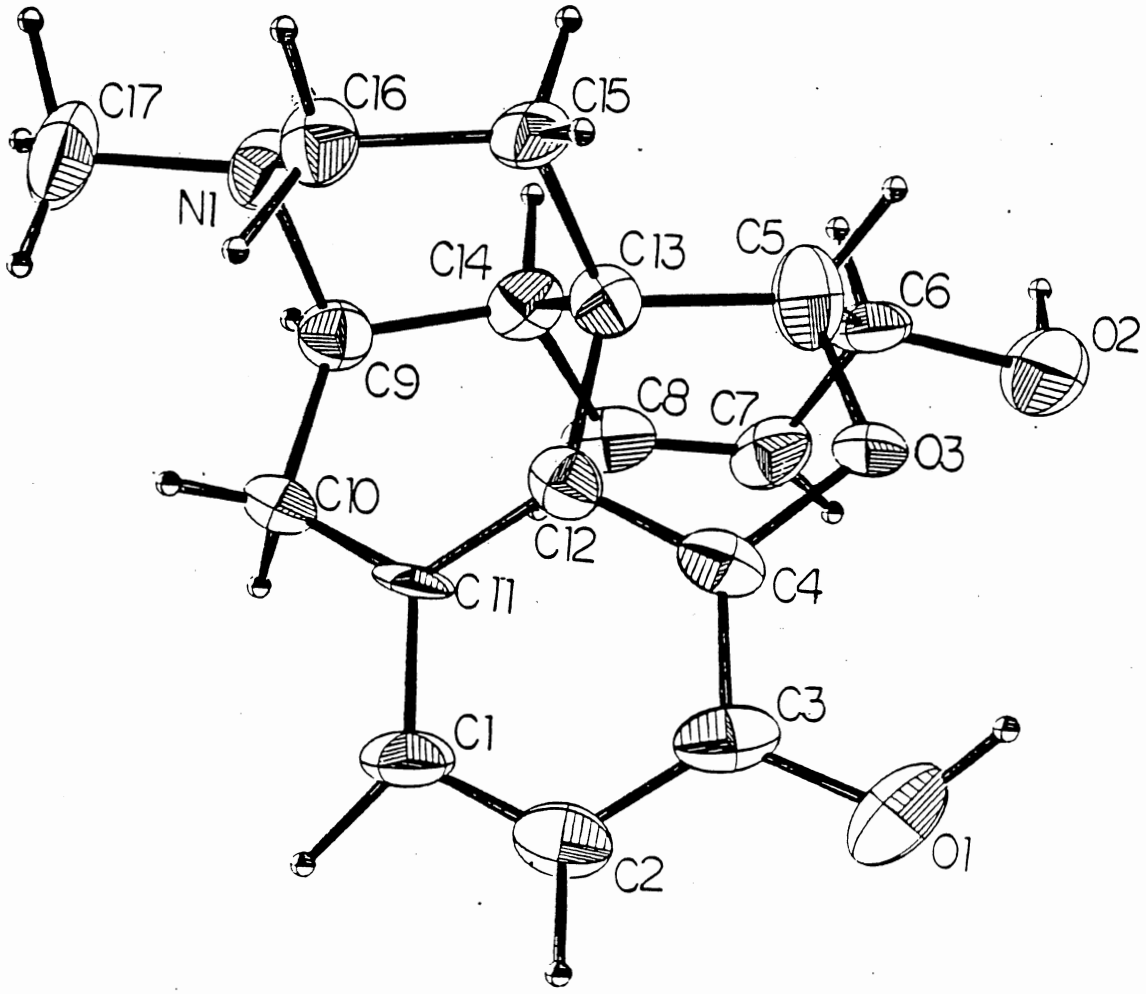


Figure 44. An ORTEP Projection of Morphine Sulfate

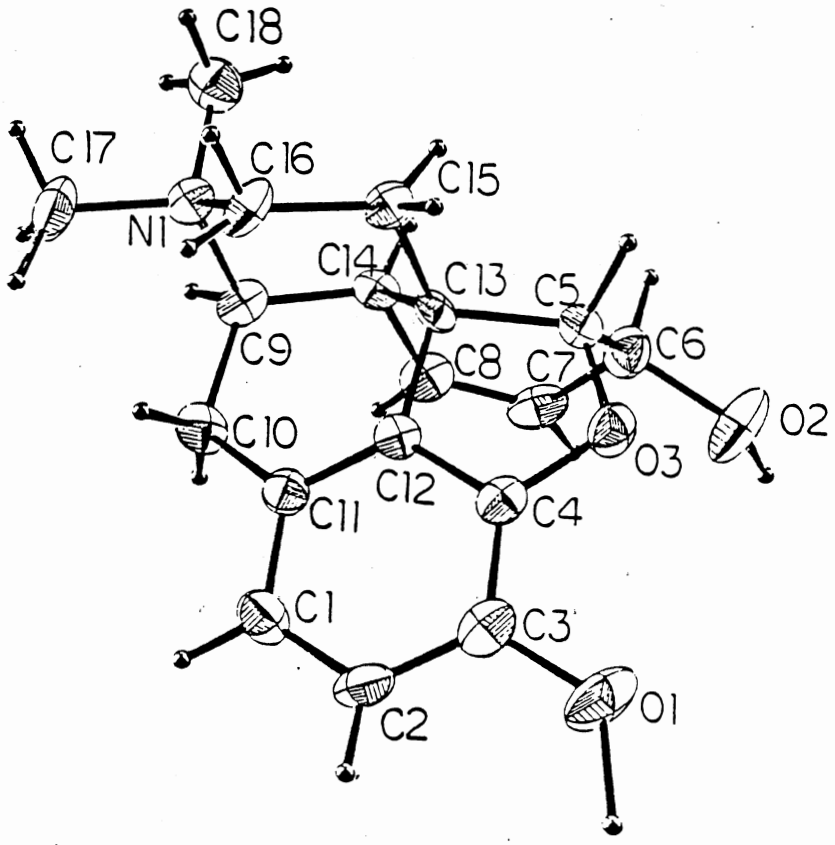


Figure 45. An ORTEP Projection of Morphine Methyliodide

morphine methyliodide and also morphine hydrate are presented in Figures 46, 47 and 48, respectively

The Structure of Compound I

Compound I was crystallized from the chloroform extract of morphine sulfate-Froehde reaction as dark purple rectangular shaped crystals. Mass spectral data (Figure 49) show that the compound has a molecular weight of 279.09 corresponding to a molecular formula of $C_{17}H_{13}NO_3$. The X-ray crystallographic study indicated a monoclinic symmetry with a $P2_1/n$ space group. Unit cell dimensions are 18.591(12), 7.774(4) and 8.762(5) A^o and the β angle is 96.60(5)^o (Table XXII). 1527 reflections from a total of 3476 points were considered valid (Appendix C). The atomic positional and thermal parameters are presented in Tables XXIII, XXIV, XXV and XXVI. The final bond lengths and bond angles between atoms in Compound I are listed in Table XXVII, with the R factor minimized to 5.8%.

An ORTEP diagram for Compound I is presented in Figure 50, and an ORTEP view of the hydrogen bonding between molecules of the Compound I is shown in Figure 51.

Solid State Circular Dichroism of Morphine Methyliodide

The SSCD of morphine hydrate not only shows a distinct difference from the spectrum for morphine sulfate as

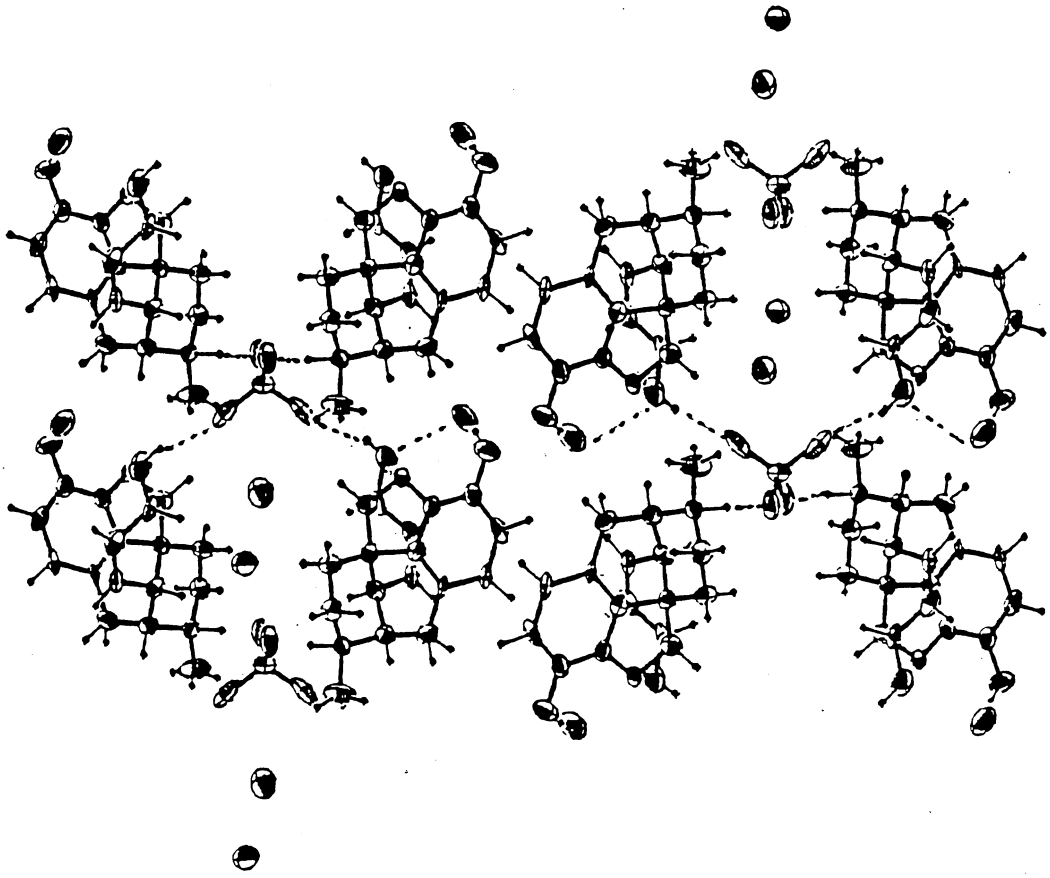


Figure 46. An ORTEP Projection of Hydrogen Bonding Network of Morphine Sulfate

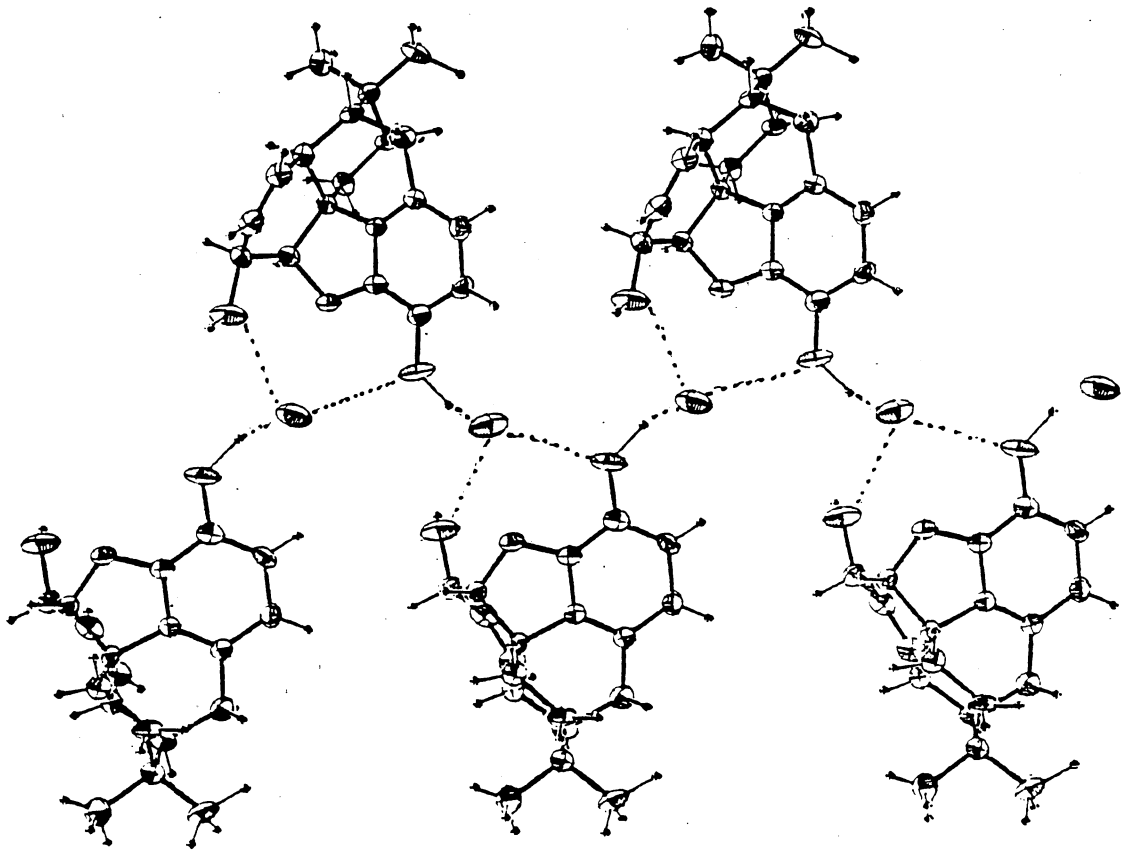


Figure 47. An ORTEP Projection of Hydrogen Bonding Network of Morphine Methyliodide

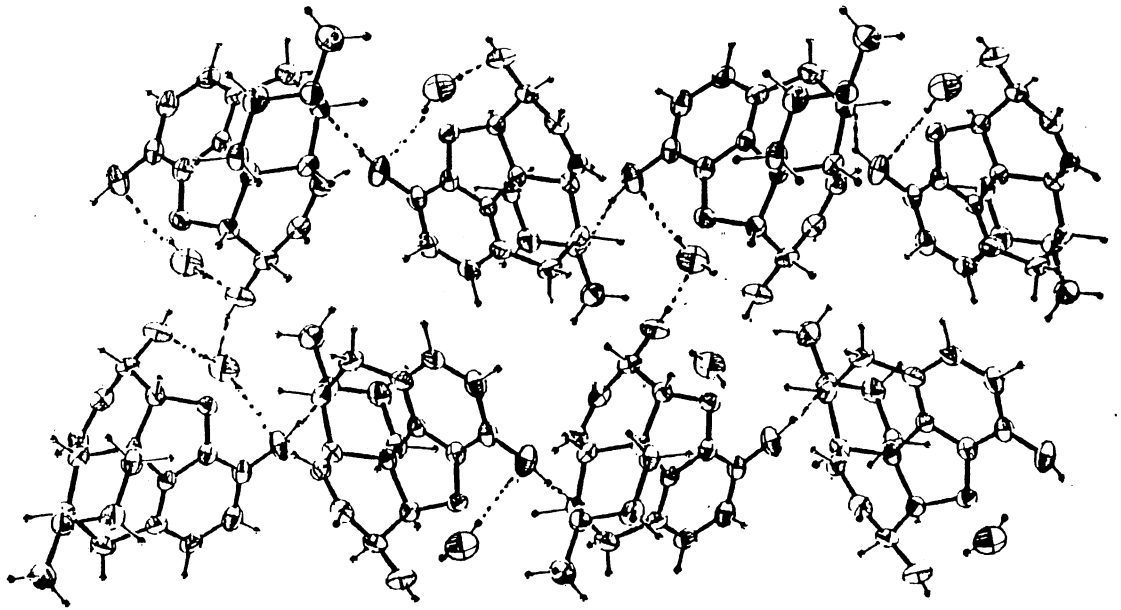


Figure 48. An ORTEP Projection of Hydrogen Bonding Network of Morphine Hydrate

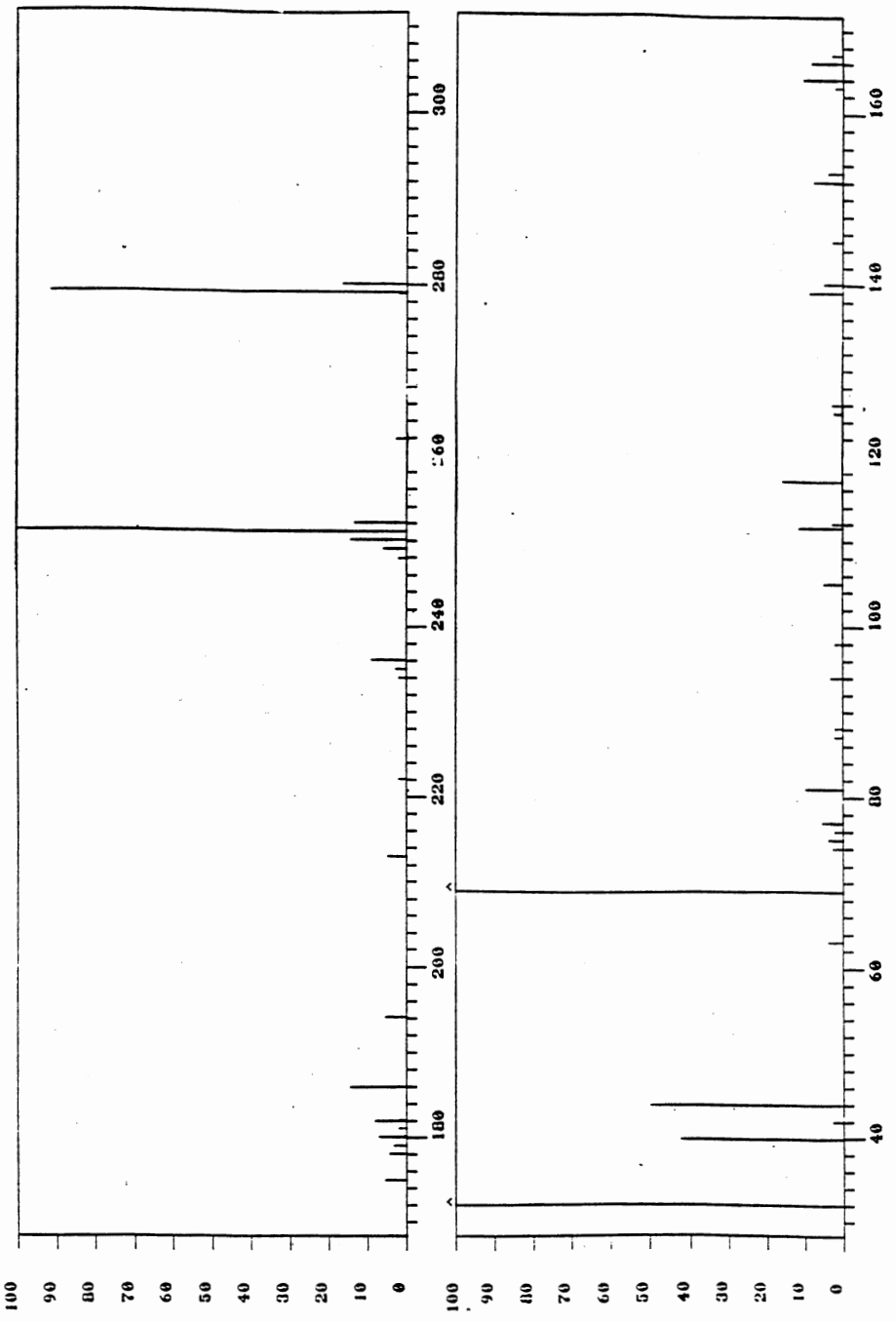


Figure 49. Mass Spectrum of Compound I

TABLE XXII

CRYSTAL DATA FOR $C_{17}H_{13}NO_3$

Formula	$C_{17}H_{13}NO_3$
MWT	279.09
a	18.591(12)A^o
b	7.774(4)
c	8.762(5)
β	96.60(5)^o
V	1258(1)A^{o3}
F(000)	587
λMok_α	0.71069A
μ_{Mok_α}	4.86
D_{calc}	1.473 g cm^{-1}
z	4
Space group	$P2_1/n$
Systematic absences	hOl, h + 1 $\neq$ 2n
	OkO, k $\neq$ 2
Obs. reflections	1527
Final R factor	5.8%

TABLE XXIII

NONHYDROGEN POSITIONAL PARAMETERS FOR $C_{17}H_{13}NO_3$

Atom	x(σ(x))	y(σ(y))	z(σ(z))
O1	-.0827(2)	-.4205(4)	0.3100(4)
O2	-.0894(2)	0.1079(5)	0.0584(4)
O3	0.0394(2)	-.3324(4)	0.4674(4)
N1	0.1326(3)	0.4277(5)	0.2505(4)
C1	-.0591(3)	0.0064(6)	0.1530(5)
C2	-.0908(3)	-.1599(6)	0.1784(5)
C3	-.0556(3)	-.2655(6)	0.2834(5)
C4	0.0147(3)	-.2213(6)	0.3746(5)
C5	0.1607(3)	-.1101(6)	0.5335(5)
C6	0.2248(4)	-.0499(6)	0.6082(5)
C7	0.2491(3)	0.1166(6)	0.5837(5)
C8	0.2089(3)	0.2231(6)	0.4822(5)
C9	0.1050(3)	0.2720(5)	0.2844(5)
C10	0.0395(3)	0.2159(6)	0.2109(5)
C11	0.0119(3)	0.0555(6)	0.2427(5)
C12	0.0487(3)	0.0578(5)	0.3478(4)
C13	0.1175(3)	-.0044(5)	0.4268(4)
C14	0.1445(3)	0.1637(6)	0.3986(5)
C15	0.2303(4)	0.4074(6)	0.4632(6)
C16	0.2079(3)	0.4689(6)	0.3019(6)
C17	0.0963(5)	0.5334(7)	0.1262(6)

TABLE XXIV

HYDROGEN POSITIONAL PARAMETERS FOR $C_{17}H_{13}NO_3$

Atom	x(σ(x))	y(σ(y))	z(σ(z))
HO2	-.053(3)	-.476(8)	0.387(6)
HC2	-.144(2)	-.199(6)	0.109(5)
HC5	0.141(2)	-.228(6)	0.551(5)
HC6	0.257(3)	-.130(6)	0.679(5)
HC7	0.298(2)	0.163(6)	0.640(4)
HC10	0.008(2)	0.283(5)	0.139(4)
H1C15	0.207(3)	0.483(6)	0.530(5)
H2C15	0.284(3)	0.424(8)	0.494(6)
H1C16	0.245(4)	0.407(9)	0.225(8)
H2C16	0.214(2)	0.602(5)	0.293(5)
H1C17	0.104(4)	0.481(8)	0.022(8)
H2C17	0.117(3)	0.645(7)	0.131(5)
H3C17	0.036(5)	0.547(10)	0.136(9)

TABLE XXV

NONHYDROGEN ATOM ANISOTROPIC THERMAL PARAMETERS FOR $C_{17}H_{13}NO_3$

Atom	10^3U_{11}	10^3U_{22}	10^3U_{33}	10^3U_{12}	10^3U_{13}	10^3U_{23}
O1	49(4)	38(2)	58(2)	-10(2)	1(2)	7(2)
O2	45(4)	54(2)	66(2)	-1(2)	-16(2)	22(2)
O3	56(4)	36(2)	50(2)	-6(2)	-3(2)	16(2)
N1	34(4)	32(2)	42(2)	-3(2)	4(2)	10(2)
C1	40(6)	38(2)	38(2)	-2(3)	1(3)	3(2)
C2	29(5)	37(2)	42(2)	-4(3)	1(2)	5(2)
C3	36(6)	34(2)	41(2)	-7(3)	10(3)	0(2)
C4	36(5)	31(2)	32(2)	3(2)	8(2)	6(2)
C5	39(6)	34(2)	36(2)	2(3)	4(2)	10(2)
C6	39(6)	44(3)	34(2)	9(3)	1(2)	8(2)
C7	28(5)	40(2)	34(2)	1(3)	4(2)	-2(2)
C8	27(6)	35(2)	38(2)	2(2)	9(2)	2(2)
C9	34(6)	24(2)	33(2)	1(2)	9(2)	7(2)
C10	30(5)	34(2)	34(2)	7(2)	1(2)	10(2)
C11	31(5)	35(2)	28(2)	2(2)	2(2)	4(2)
C12	22(5)	28(2)	29(2)	4(2)	6(2)	5(1)
C13	35(5)	27(2)	26(2)	1(2)	10(2)	3(1)
C14	24(5)	31(2)	31(2)	3(2)	2(2)	3(2)
C15	51(6)	37(2)	48(2)	-7(3)	2(3)	2(2)
C16	40(6)	40(2)	53(3)	-13(3)	5(3)	16(2)
C17	68(8)	31(2)	45(3)	-2(3)	5(3)	13(2)

$$\exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*]$$

TABLE XXVI

HYDROGEN ISOTROPIC THERMAL PARAMETERS FOR $C_{17}H_{13}NO_3$

Atom	10^2U	Atom	10^2U
HO1	9(2)	HC2	4(1)
HC5	4(1)	HC6	5(1)
HC7	4(1)	HC10	3(1)
H1C15	6(2)	H2C15	8(2)
H1C16	12(3)	H2C16	4(1)
H1C17	9(2)	H2C17	4(1)
H3C17	13(4)		

TABLE XXVII

BOND LENGTHS(A°) AND ANGLES(°) FOR $C_{17}H_{13}NO_3$

C1-O2	1.233(6)	C1-C1	1.448(7)
C1-C11	1.505(8)	C2-C3	1.345(7)
C3-O1	1.337(6)	C3-C4	1.493(8)
C4-C12	1.450(7)	C4-O3	1.238(8)
C5-C6	1.374(8)	C5-C13	1.421(6)
C6-C7	1.396(7)	C7-C8	1.372(7)
C8-C14	1.407(7)	C9-C10	1.391(8)
C9-C14	1.443(6)	C10-C11	1.389(7)
C11-C12	1.396(6)	C12-C13	1.443(8)
C13-C14	1.432(6)	C8-C15	1.502(7)
C15-C16	1.505(7)	N1-C9	1.360(6)
N1-C16	1.457(8)	N1-C17	1.466(7)
C1-C2-C3	118.4(5)	C2-C3-C4	123.6(5)
C2-C3-O1	120.4(5)	O1-C3-C4	116.0(4)
C3-C4-O3	115.2(4)	C3-C4-C12	119.1(4)
C12-C4-O3	125.7(5)	C11-C12-C4	118.0(5)
C13-C12-C4	123.5(4)	C11-C12-C13	118.4(4)
C10-C11-C12	122.3(5)	C1-C11-C12	121.2(4)
C1-C11-C10	116.4(4)	C11-C1-C2	119.6(4)
C13-C5-C6	120.7(4)	C5-C13-C12	123.5(4)
C5-C13-C14	117.2(5)	C12-C13-C14	119.3(4)
C5-C6-C7	121.4(5)	C6-C7-C8	119.8(5)
C7-C8-C14	120.4(4)	C8-C14-C13	120.3(4)
C7-C8-C15	121.0(5)	C8-C14-C9	120.3(4)
C13-C14-C9	119.4(4)	C9-C10-C11	121.1(4)
C10-C9-C14	119.4(4)	N1-C9-C10	120.9(4)
N1-C9-C14	119.8(4)	C14-C8-C15	118.4(4)
C8-C15-C16	111.0(4)	C15-C16-N1	111.9(5)
C9-N1-C17	120.6(4)	C9-N1-C16	120.0(4)
C16-N1-C17	116.8(4)		

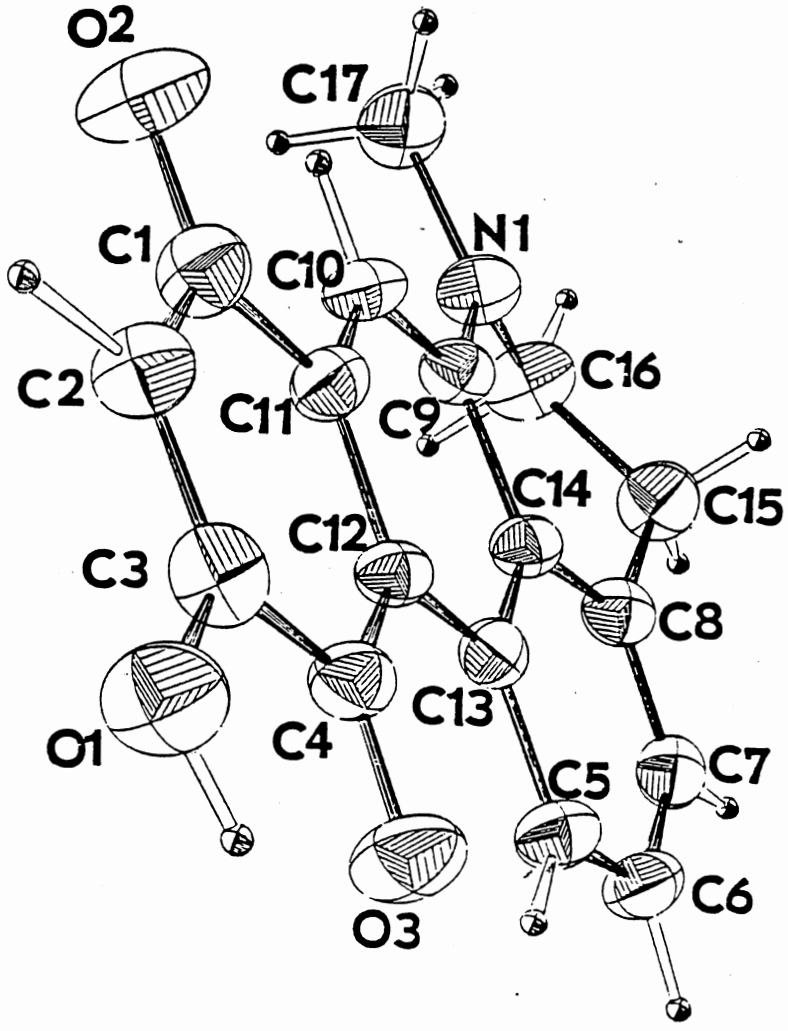


Figure 50. An ORTEP Projection of Compound I

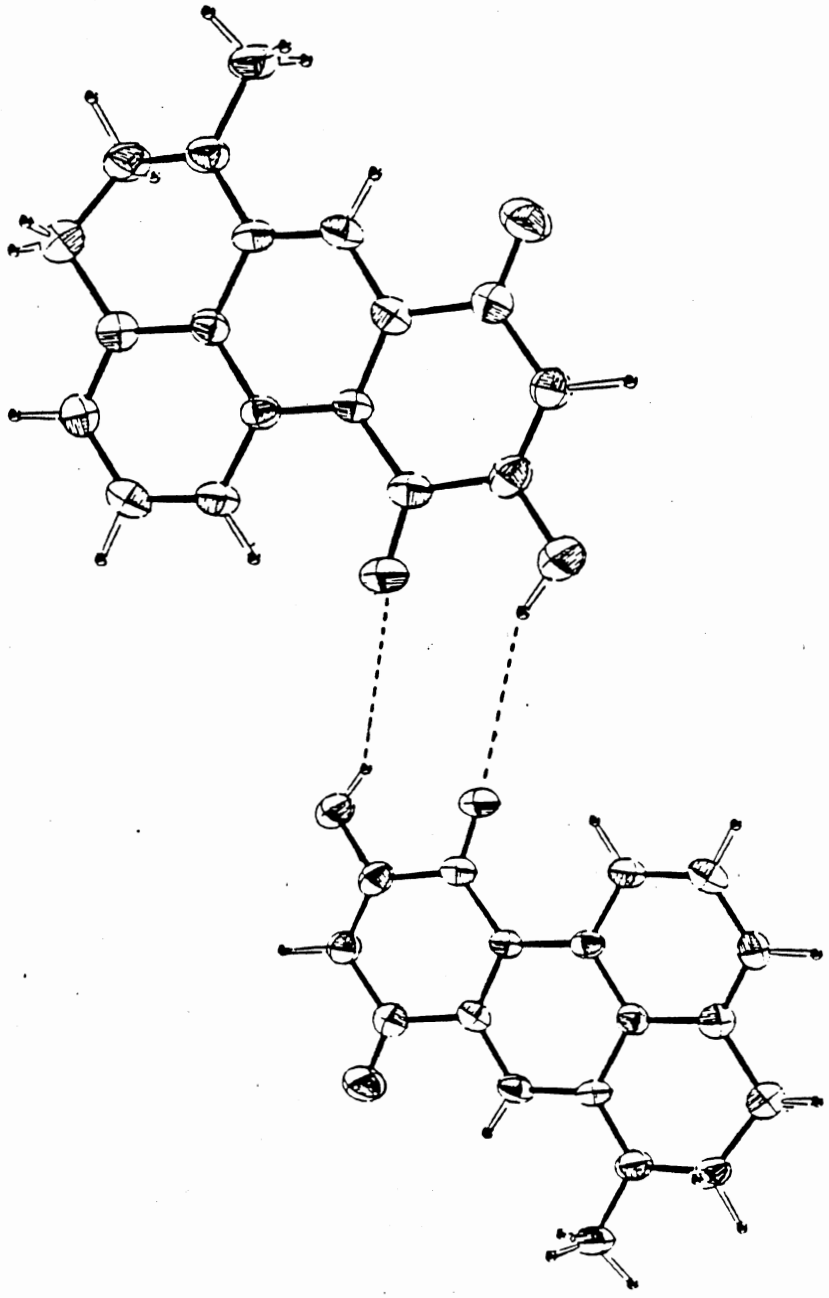


Figure 51. An ORTEP View of Hydrogen Bonding of Compound I

reported earlier but also from that for morphine methyl-iodide. The salts on the other hand have qualitatively similar SSCD spectra showing a positive band with λ^{+}_{max} around 255 nm and a negative band with λ^{-}_{max} around 295 to 300 nm. For morphine hydrate the SSCD is all positive with a shoulder around 297 nm and a band with λ^{+}_{max} of 260 nm.

The SSCD spectra of these three compounds (Figure 52) are different from the spectra of the compounds in the aqueous solutions. All the spectra of the compounds in distilled water possess the same CD patterns with slightly different values for λ^{o} (Figure 53). The characteristic wavelengths of these three morphine molecules are tabulated in Table XXVIII for easy comparison.

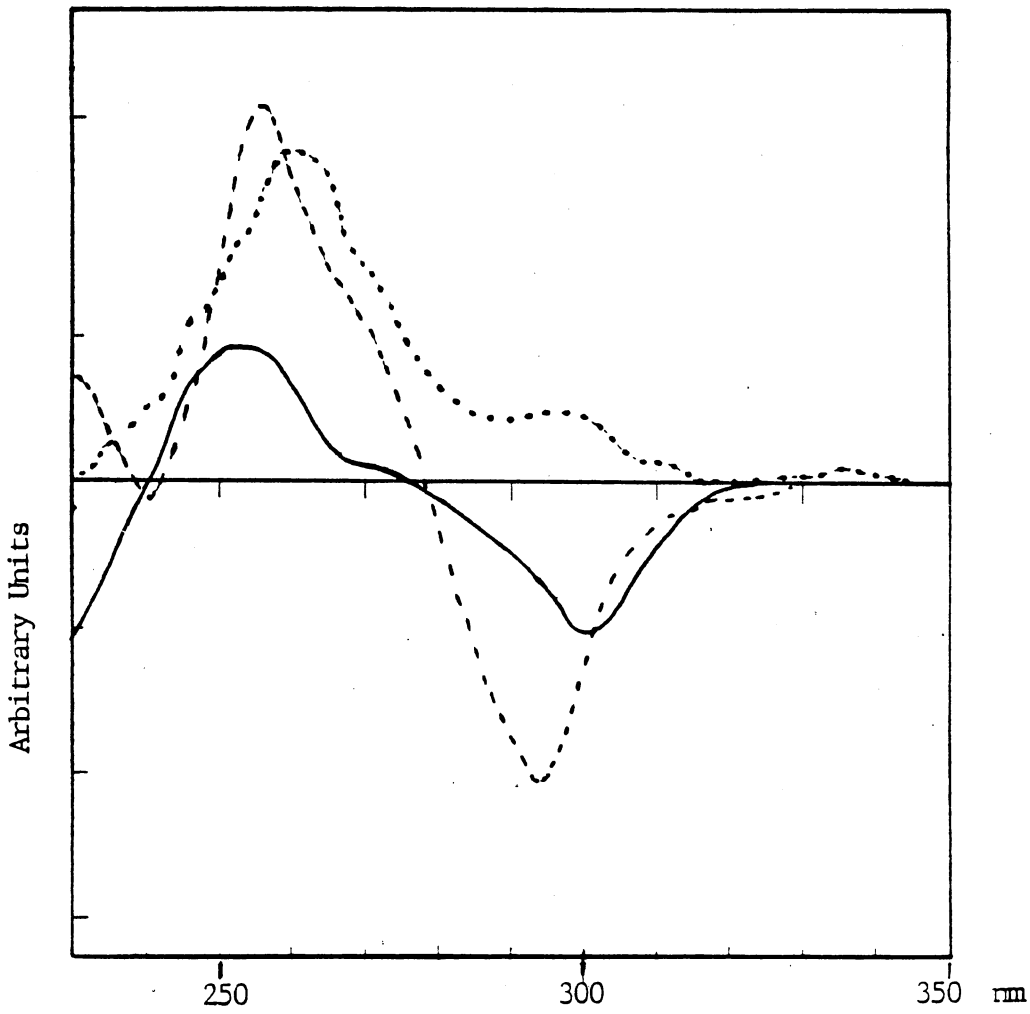


Figure 52. SSCD Spectra of Morphine (···), Morphine Sulfate (——) and Morphine Methyliodide (---)

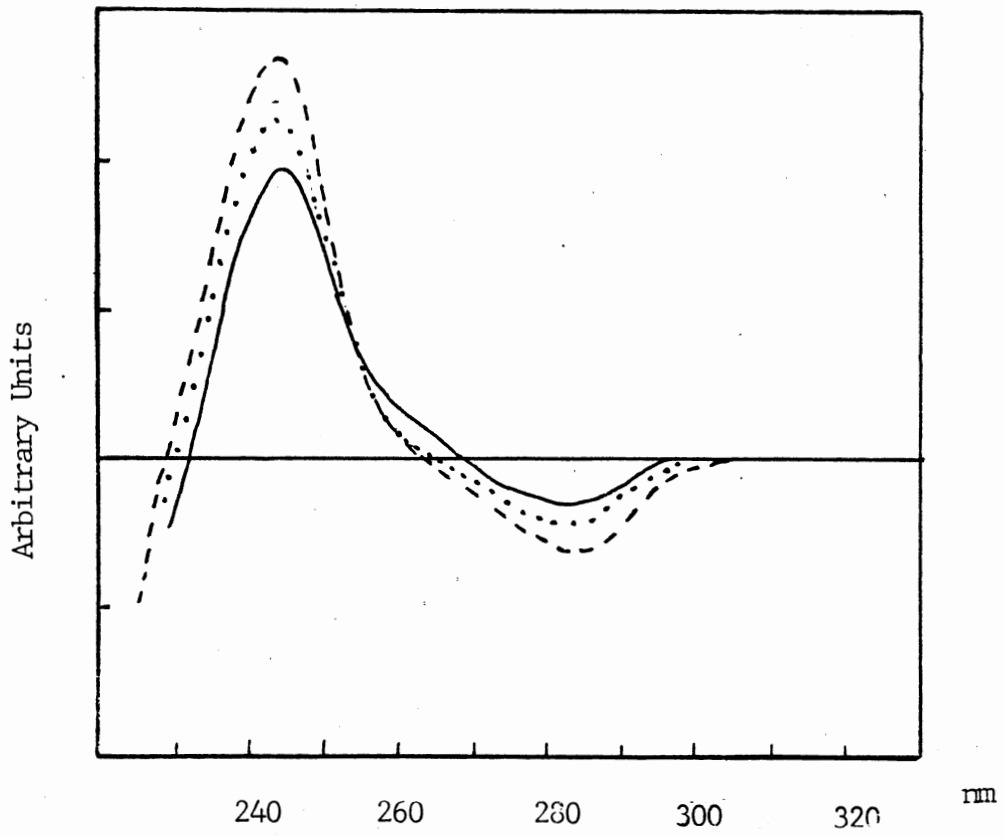


Figure 53. CD Spectra of Morphine (···), Morphine Sulfate (——), and Morphine Methyl-iodide (---) in Distilled Water

TABLE XXVIII

SSCD AND CD DATA OF MORPHINE AND ITS SALTS

Compound	λ_{max} (nm)	
	SSCD	CD
Morphine	297^{+}(sh), 260^{+}	243^{+}, 285^{-}, 270^{o}
Morphine Sulfate	302^{-}, 254^{+}, 271^{o}	244^{+}, 284^{-}, 267^{o}
Morphine Methyl-iodide	294^{-}, 256^{+}, 278^{o}	244^{+}, 285^{-}, 264^{o}

+ indicates a positive band
- indicates a negative band
o indicates a crossing point
(sh) indicates a shoulder band

CHAPTER V

DISCUSSION

The purpose of this research was to study the oxidation-reduction reactions of morphine in three different media: basic, neutral and concentrated sulfuric acid solutions. Product identification is the critical theme of the work and is described for each system in turn.

Oxidation of Morphine in Basic Solution

The principal product of this reaction proposed previously (11) is the dimeric compound pseudomorphine. Working from this assumption a NMR study was done for structural confirmation.

Results from a ^{1}H NMR of morphine sulfate and pseudomorphine in DMSO(d6) show that the only significant changes in these two spectra occur in the region of the aromatic hydrogens. Since there are only two aromatic hydrogens in morphine the spectrum consists of a quartet of peaks. The pseudomorphine spectrum on the other hand consists of a singlet in this region. The integrations of those peaks confirm that the relative numbers of aromatic hydrogen atoms are two for morphine and one for pseudomorphine. The implication is that dimerization occurs via the aromatic

rings, by a combination yet undetermined but involving C1 or C2 and C1' or C2', a total of three possibilities.

Both compounds contain seventeen different carbons but only those in the region of the unsaturated carbons in the ^{13}C NMR spectra show any significant difference in the positions of some of the chemical shifts and off-resonance peaks. This is further confirmation of dimerization via the aromatic nuclei, but it still does not reveal which carbons are involved in the link. The possibility of a C1 to C2' bond is, however, eliminated from consideration. The remaining two possibilities for dimerization are the symmetrical linkages between C1 and C1' or C2 and C2' (Figure 54).

To distinguish between these two possible structures, comparisons were made of th3 ^{13}C NMR spectra for morphine, codeine, and simpler model compounds, namely phenol and o,o'-biphenol and anisole and m,m'-bianisole. Assignments of the chemical shifts for C1 and C2 in morphine sulfate were confirmed in a comparison with codeine. The methyl group on C3 of codeine produces a large ortho-effect on C2 causing it to move upfield relative to the C2 resonance in morphine sulfate. Accordingly the peaks at 119.05 ppm and 117.10 ppm in the fully decoupled ^{13}C spectrum of morphine are assigned to the C1 and C2 resonances, respectively. The corresponding positions in codeine are 118.15 ppm and 112.91 ppm. The assignments are in accord with the results of Carroll et al. (43).

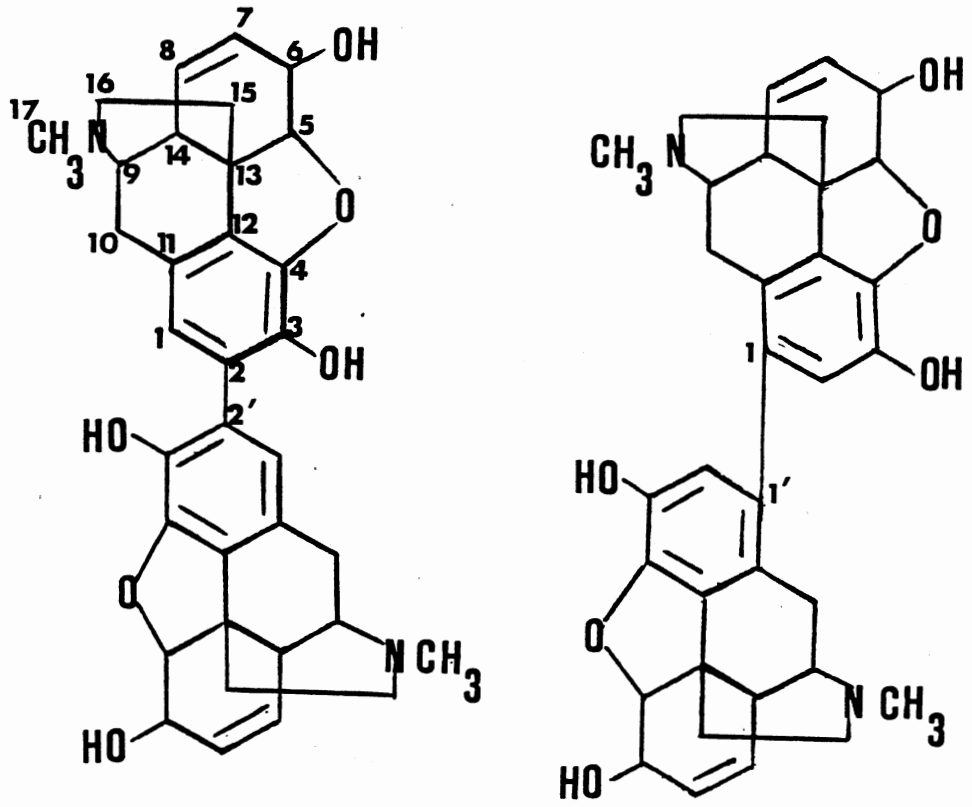


Figure 54. The Possible Structures of Pseudomorphine

The ^{13}C NMR fully decoupled and off-resonance spectra of pseudomorphine identify the resonance at 121.0 ppm with a tertiary carbon atom and the peak at 124.3 ppm with a quaternary carbon atom, but does not distinguish which one is C1 and which is C2. In forming the quaternary carbon the aromatic proton has been substituted by a monomeric morphine. The chemical shift for the carbons forming the link would be expected to move to lower field compared to the corresponding carbon in morphine on substitution. This was confirmed from the C spectra of the four model compounds (Figure 55).

In 2 the C2 resonance peak was shifted downfield by 10.4 ppm on substitution relative to C2 on phenol. In addition the position of C1 on phenol was moved upfield and C6 was moved downfield on substitution to produce the dimer. For the anisole analog of the 1,1'-dimer, C3 shifted downfield by 12.35 ppm from the position on anisole on substitution. By analogy with these results it is concluded that a downfield shift of approximately 10 ppm for the bridging carbons might be anticipated when morphine is oxidatively dimerized to pseudomorphine. The largest downfield shift observed when the ^{13}C spectra of morphine and pseudomorphine are compared is 7.2 ppm. This would require a reversal in the assignments of the C1 and C2 resonance peaks in the spectrum of pseudomorphine compared to morphine and is the most reasonable conclusion based upon the data for the model compounds. Bonding

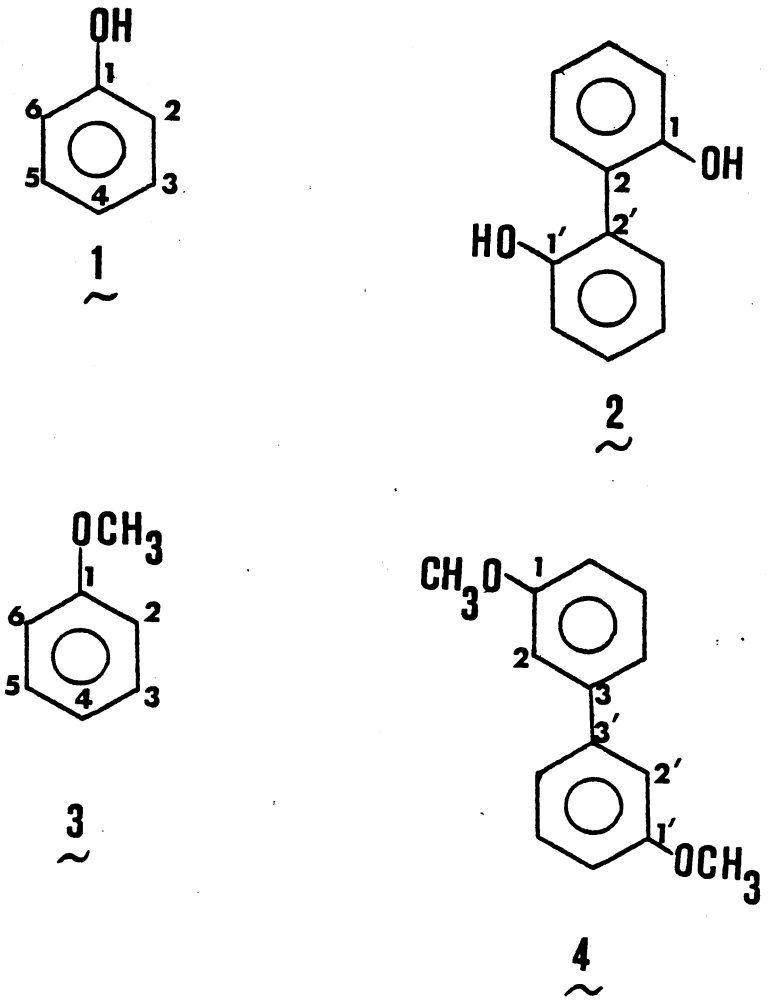


Figure 55. Structures of Phenol, o,o'-Biphenol, Anisole and m,m'-Bianisole

between C2-C2' is consistent with this interpretation. The shifts observed for C3, C11 and C12 are also consistent with a new substituent at C2. In contrast, if the dimerization position was C1-C1', the ortho-effect of the hydroxyl gorup would produce an upfield shift for both C2 and C11 contrary to what is observed.

In conclusion, therefore, the evidence from the ^{13}C NMR study supports the structural model in which the dimerization occurs at the carbon C2-C2' positions.

Oxidation of Morphine and Pseudomorphine by Inorganic Ions in Aqueous Solutions

In the previous section the oxidation of morphine in basic solution by either air or by ferricyanide ion was described. The only product is pseudomorphine if the oxidant is present in stoichiometric proportions.

The presence of pseudomorphine as a product of the oxidation reaction is easily confirmed from the CD spectrum of the solution. For each of the reactions in this section the product was again confirmed to be pseudomorphine from the measured CD spectrum, if stoichiometric quantities were used. The higher oxidation product (HOP), yet uncharacterized, is produced whenever the oxidant is present in large excess. HOP can also be distinguished by its CD spectrum. Accordingly the contributing half reactions may be formally described by the equations:

$$OA + ne^- \rightleftharpoons RA$$

$$2\ M + 2\ OH^- \rightleftharpoons M_2 + 2H_2O + 2e^-$$

and

$$M_2 \rightleftharpoons (HOP) + me^-$$

OA and RA are the oxidized and reduced forms of the inorganic reagent, and M and M_2 are morphine and pseudomorphine, respectively. Oxidative dimerization is a two electron transfer process of uncertain mechanism. It is represented here as a basic reaction involving OH^- since the reaction readily proceeds in aqueous alkali, but not in aqueous acid. Other alternatives may be possible, such as a free radical reaction or a hydride transfer, but are considered to be less likely.

Eight potential oxidizing agents were selected whose standard reduction potentials (E^o) ranged over 1.56 volt, and used to estimate reduction potentials for the morphine and pseudomorphine half reactions (Table XXIX). The morphine column in Table XXIX describes the results observed when 1:10 mole ratio of morphine to inorganic ions were used. For the last column, the starting material was pseudomorphine and the OA was present in large excess. Since the drug concentrations were on the order of 5*1E-5 M, the E^o data alone is not informative. Corrections to the E values in Table XXIX were made using the Nernst equation and the simple assumption that:

a) the oxidation products are the same for all the reactions.

TABLE XXIX

REDUCTION POTENTIAL DATA OF METAL IONS IN THE NEUTRAL REDOX REACTIONS

Electrode Reaction	E^{o}(volt)	Result	
		Morphine	Pseudo-morphine
$Ag + e^{-} \rightleftharpoons Ag$	0.799	R	R
$MnO_4^{-} + e^{-} \rightleftharpoons MnO_4^{-2}$	0.564	R	R
$Fe(CN)_6^{-3} + e^{-} \Downarrow Fe(CN)_6^{-4}$	0.36	R	R
$Cu^{+2} + 2e^{-} \rightleftharpoons Cu$	0.337	NR	(R)
$Pb^{+2} + 2e^{-} \rightleftharpoons Pb$	-.126	NR	NR
$Ni^{+2} + 2e^{-} \rightleftharpoons Ni$	-.250	NR	NR
$Cd^{+2} + 2e^{-} \rightleftharpoons Cd$	-.403	NR	NR
$Zn^{+2} + 2e^{-} \rightleftharpoons Zn$	-.763	NR	NR

NR = non-spontaneous reaction
R = spontaneous reaction
(R) = reaction goes very slowly

b) at equilibrium, oxidation is effectively quantitative.

c) with OA in large excess,

$$[OA]_{final} \cong [OA]_{initial}.$$

The recution potential for the morphine half reaction is intermediate between that for ferricyanide and for Cu(II) ion; that is, between 0.42 volt and 0.24 volt after correction for concentration. For pseudomorphine there was some evidence for oxidation by Cu(II) ion, but the process was kinetically very slow, CD evidence for HOP developing over a period of several days. The lack of availability of an OA whose E^o value lies between 0.33 and -0.1 volt prevented a better estimate being obtained.

The results are consistent with the reported E^o values for oxidizing agents which function in basic media, such as MnO_4^- (E^o = 0.56 volt) and dissolved oxygen (E^o = 0.41 volt).

Oxidation of Morphine Sulfate and Apomorphine Hydrochloride in Concentrated Sulfuric Acid Solution

Concentrated sulfuric acid has excellent solvent properties, is a powerful dehydrating agent, a strong acid, a good oxidizing medium, and has the ability to stabilize free radicals (44). Even in the absence of the inorganic oxyanions used as oxidizing agents in the color

test reagents, the solvent alone, or in combination with dissolved oxygen, could produce a number of concurrent and/or consecutive reactions with morphine and apomorphine. Morphine has a pentacyclic structure and apomorphine is tetracyclic. There is a possibility that the latter is an intermediate in the reaction of morphine.

There is an immediate reaction on solution of morphine in concentrated sulfuric acid evidenced by inversion of the CD spectrum from that observed in dilute aqueous acid. Dilution of the concentrated sulfuric acid with water does not reverse the CD spectrum indicating that an intermediate product has been formed. There is no evidence for free radicals in the solution (45). Apomorphine on the other hand shows no change in the CD spectra between dilute and concentrated acid conditions.

As time progresses the morphine reaction sequence changes the color of the solution from brownish-orange to green to brownish-gray and finally to brownish-purple. For apomorphine the color sequence is from clear to purple gray and finally to brownish pink. The color of both solutions are very similar after two to four weeks when the reactions are considered to be complete. This does not mean that the compositions of both are identical but it strongly supports the idea that apomorphine is an intermediate in the morphine reaction.

The reactions which occur when the inorganic oxyanions are added appear to be similar to those already

described and the analyses of final solutions give comparable results. Reaction times are much shorter. The evidence supports the involvement of oxygen in the reactions when the compounds are reacted in only the solvent. For these reactions the ESR evidence supports the existence of free radical intermediates when the inorganic oxyanions are present, but only for morphine and not apomorphine (45).

Changes in the UV and CD spectra with time lend further support to the mechanism which includes apomorphine as an intermediate. The spectra of the final solutions under both reaction conditions are not exactly alike in quantitative terms but this might be explained as the same products being present in different amounts. For the color test reagents the reduced forms of the oxyanions may also contribute to the observed UV-visible spectra.

Chloroform extracts from the final morphine products in both acid alone and with color reagents added produce the same UV-visible spectrum. The same is true for the apomorphine reactions. Chloroform does not extract the inorganic ions. Optical activity is lost since none of the extracts give a CD spectrum.

Separation by TLC produces three spots in every case indicating the presence of at least three components. According to the mass spectrometric data, the heaviest component has a molecular weight equal to 325.25 g/mole.

Compound I has a molecular weight of 279.1 g/mole, and its structure was confirmed by X-ray diffraction. The Rf value of 0.34 is consistent with its being more polar than the other two components. Although there is some correspondence between the Rf values of the middle component and that for apomorphine alone, the product can not be unreacted apomorphine because the CD result is negative.

A possible mechanism for the formation of Compound I which includes apomorphine as an intermediate is given in Figure 56.

X-ray Structural Analysis

Structural Comparison of Morphine Sulfate and Morphine Methyliodide

Two reasons existed for initiating the solid state structural study of the morphine derivatives. First, the CD spectra of morphine and the sulfate salt are inverted in sign when the aqueous solution conditions are changed from acid to base. This implies a chirality change in the molecule which can not be interpreted without an x-ray structural analysis. Morphine sulfate is readily crystallized into a suitable form for diffraction studies. All attempts to prepare a metal morphinate salt so far have failed. The methyliodide derivative was prepared to explore the effects of N-substitution on the conformation of the four chiral center backbone of the morphine structure.

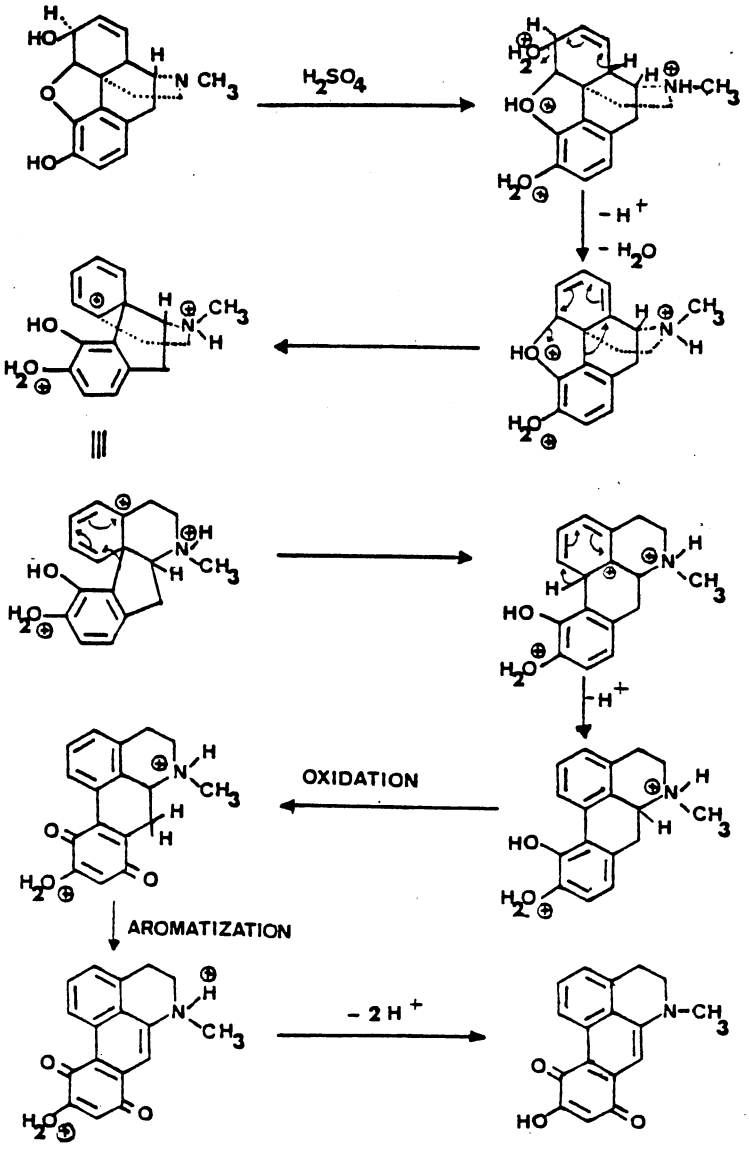


Figure 56. Postulated Mechanism of Formation of Compound I

The second reason for this study relates back to earlier work on solid state CD (31). In that study the CD spectra of morphine and morphine sulfate were seen to be of opposite signs. The rotational change must be either a consequence of a molecular conformational change or a change in the packing arrangement in the crystal, or perhaps both. A structural determination for morphine free base had already been reported (46); this is the first report for morphine sulfate and morphine methyliodide.

From the X-ray data all the bond distances and bond angles for morphine methyliodide monohydrate (I) and morphine sulfate trihydrate (II) are similar. In (I) the average bond angles about the nitrogen atom bonded to four carbon atoms show no significant distortion from the 109 angle expected for sp^3 hybridization. In (II) where the nitrogen is bound to one hydrogen and three carbons, the C-N-C angles show a larger average (112.6°) which may be expected considering the volumes of carbon and hydrogen and the expected compression of the C-N-H angles.

In both molecules ring C displays a distorted boat geometry and ring E is in the chair conformation. The conformation for ring D is the same for both salts. In (II) the methyl group, C17, occupies an equatorial position relative to ring E, the axial position being occupied by a hydrogen from H_2SO_4. Comparisons may be drawn between these two salts and the hydrochloride salt

(47). While structural details for the rest of the carbon skeleton are similar to those of the title structures, those of ring E of the hydrochloride more closely resemble those of the sulfate salt (II) than the methyliodide salt (I).

The parking arrangement of the molecules in the methyliodide analog involves a linear chain of hydrogen bonding which extends throughout the crystal parallel to the a axis of the unit cells by virtue of the phenolic hydrogen (HO1) being bonded to the oxygen of the neighboring water (O4) molecules (HO1-O4 distance equal to 1.517(11) A^{o}). The water hydrogens bridge between the phenolic oxygen (O1Ii)) and the hydroxyl oxygen (O2(i)) of another adjacent morphine molecule (O4-O1(i) = 3.08(2) A^{o}, O4-O2(i) = 2.86(1) A^{o}) which is symmetry related by x, y, z and (1/2) + x, (1/2) - y, 1 - z. The network then extends to a morphine at 1 + x, y, z and is repeated throughout the crystal which traces out a clockwise turn on progression from the origin along the a direction. There is no hydrogen bonding involving the iodide ion.

On the other hand, the sulfate anion of morphine sulfate trihydrate is involved in hydrogen bonding. An oxygen (O111) of the sulfate group is hydrogen bonded to a nitrogen proton (HN1) of one morphine with a hydrogen bonded distance of 1.71(6) A^{o}, and a second sulfate oxygen (O112) is hydrogen bonded to a hydroxyl hydrogen (HO2(i)) of an adjacent morphine molecule (O112-HO2(i) =

2.39(15) A^{o}) with symmetry related by x, y, z to 1+x, 1-y, 1-z which then in turn continues in a chain in the a direction. An oxygen from water (O113) is hydrogen bonded to a phenolic hydrogen (HO1) at a hydrogen bonded distance of 1.87(15) A^{o} and one hydrogen from the water molecule is bonded to a hydroxyl oxygen (O2) of the morphine. The hydrogen for the water molecule is not actually located but the observed O113-O2 distance is 2.862(9) A^{o}. A clockwise turn similar to that in the methyliodide salt is again observed to occur along the a directional axis. The other two water molecules (O114, O115) in morphine sulfate trihydrate are within hydrogen bonding distance from each other (O114-O115 distance equal to 2.783(9) A^{o}) but do not reach contact distance with the morphine molecules.

To complete the comparison of the X-ray structural information for the salts and morphine free base, the data from the earlier work by Bye on morphine monohydrate were used to obtain comparable projections. The conformational arrangements reported here for ring D and E are repeated in the morphine free base structure. The influence of the N1 substitution on the local geometry is negligible. Two types of hydrogen bonding networks exist in morphine monohydrate crystals. One network consists of strong hydrogen bonded interactions along the b axis and displays a clockwise turn as viewed down the b axis from the origin. The atoms involved are a nitrogen (N1) on one morphine molecule

and the hydrogen of a phenolic group (HO1(i)) on another morphine molecule (N1-HO1(i) distance = 1.57(3) A^{o}).

These are symmetry related by x, y, z and -x, (1/2) + y, (1/2) - z. So the chain of morphine molecules directly hydrogen bonded to other morphine molecules extends along the y axis. The second network of hydrogen bonding involves a water molecule and is relatively weak when compared to the first network. The hydrogens (H1O4 and H2O4) of the water molecule bridge between the hydroxyl (O2) and phenolic oxygen (O1) atoms on the same morphine unit. The hydrogen bonding distances H1O4-O2 and H2O4-O1 are equal to 1.97(4) A^{o} and 2.27(5) A^{o}, respectively, and are typical of rather weak interactions. The oxygen of the same water molecule is also bonded to a hydroxyl (HO2(i)) of another morphine molecule and is symmetry related by x, y, z and (-1/2) + x, (1/2) - y, 1 - z. The O4-HO2(i) distance in this case is 1.91(3) A^{o}. This network extends throughout the crystal along the a axis.

Considering these structural observations collectively, the reason for the inversion of the negative 286 nm Cotton band in the SSCD spectrum of morphine free base is difficult to interpret. One can eliminate from consideration the idea that the free base has a unique molecular conformation since all are essentially alike. Similarly, a conformation common to all three excludes from consideration any structural changes which might have accompanied the chirality changes around the N1 atom. Long range

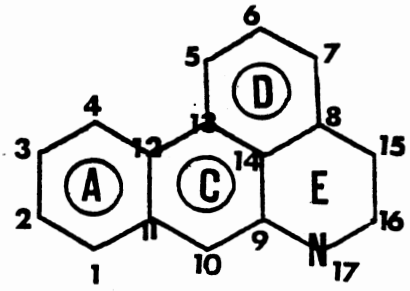
crystal packing arrangements have analogous clockwise patterns established by hydrogen bonded networks in all three crystals.

Two differences exist but how these might affect the chirality in a SSCD measurement is not clear. First, the details of the primary hydrogen bonding networks are different in each case. For the salts either the sulfate ion or water is involved in bonding to the morphine moiety. For the free base the morphine molecules are directly bonded. The secondary network, which is much weaker involves both inter- and intramolecular hydrogen bonding. Secondly, the hydrogen bonding helical arrangement in the salts occurs along the short axis of the unit cell, while in the free base the helix is oriented along the long axis. Although the rotation of the helix is clockwise in every case, the pitch of the spiral is longer in the free base. It is known for example that the CD activity of cholesteric liquid crystals is affected by the pitch of the helical arrangement (51). It is also conceivable that the anisotropic crystal arrangements of the aromatic chromophores might orient the direction of polarization of the electronic transitions at different angles relative to the incident beam. The sign of a CD signal is determined by the difference in the molar absorbances of the left and right circularly polarized components. A change in sign might reflect a spatial effect on the relative rotatory strengths of the transitions. Anisotropy is lost

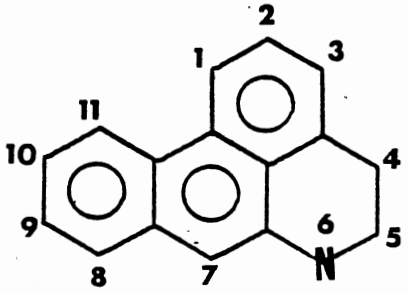
when the crystals are dissolved in polar and non-polar isotropic solvents.

The Structure of Compound I

The numbering system adopted for the non-hydrogen atoms of Compound I is either based upon that for aporphine compounds (48) or 4H-dibenzo(de,g)quinoline (49) as shown in Figure 57. The molecule shows virtual coplanarity for all non-hydrogen atoms except C15, C16 and C17. The average deviation from the plane of C1 to C14, N1, O1, O2 and O3 is 0.04061 A^{o}. Atoms C15, C16 and C17 on the nitrogen ring deviate above the plane 0.3143, 0.3597 and 0.1812 A^{o}, respectively. Since this molecule is derived from morphine, the numbering and arbitrary naming of the rings as A, C, D and E is based on the morphine system. In ring A, C2-C3 (1.345 A^{o}) and C12-C11 (1.396 A^{o}) bond distances are typically aromatic (cf benzene) characteristic whereas C1-C11 (1.505 A^{o}) and C3-C4 (1.493 A^{o}) bond distances are characteristic of normal C-C single bond (1.53 A^{o}). The C-O bond distances are consistent with a C=O grouping on C1 and C4 and C-OH on C3 (C-O distances equal to 1.233, 1.238 and 1.337 A^{o}, respectively). The bond angles in the ring are in the range of 118.0 to 123.6^{o}, close to the characteristic value for sp^2 hybridization. Ring C and D are typically aromatic. Ring E, which by deduction is the only non-aromatic ring has a N1-C16 bond distance equal to 1.457 A^{o} which approximates to the



APORPHINE



4H-DIBENZO [de,g] QUINOLINE

Figure 57. The Numbering System of Compound I

normal C-N value (1.475 A^{o}) and the bond distance for C15-C16 (1.505 A^{o}) is typical of a C-C single bond. The bond angles C15-C16-N1 (111.9°) and C8-C15-C16 (111.0°) are also representative of sp^3 hybridization as expected.

The molecules are interconnected to one other by hydrogen bonds between the hydroxyl hydrogen on C3 of one molecule and the carbonyl oxygen on C4 of another molecule. The O-H hydrogen bond distance is 2.09 A^{o}.

Conclusion and Suggestions for Further Work

From literature reports (3, 11) and the experimental results of this study, the reactions of morphine in both aqueous neutral and basic solutions with the oxidizing agents $K_3Fe(CN)_6$, $KMnO_4$, and some metal ions produce the same products. The principal oxidation product is pseudomorphine which can undergo further oxidation when the conditions allow. The second oxidation product HOP can be differentiated by its CD spectrum from pseudomorphine. The details of the second oxidation and the identity of HOP are unknown. The uncertainty about the mode of dimerization of two morphine molecules to produce pseudomorphine has been tentatively resolved and is believed to occur by bridging between the C2-C2' carbon atoms of the aromatic rings. This conclusion is in agreement with the normal coupling of phenol compounds which usually takes place at positions which are either ortho or para to the -OH

positions (50). The stoichiometry of the reduction-oxidation reaction suggests that two protons are lost and two electrons are transferred in forming one molecule of pseudomorphine from two molecules of morphine.

On the other hand, the oxidation of morphine in concentrated sulfuric acid, a common solvent in color test reagents, produces totally different products. The evidence from CD, UV-visible and TLC data, strongly suggests that the products of the reactions in either the acid alone or in the presence of the color test reagents are the same, and that apomorphine is an intermediate. The reactions occur much more rapidly when the molybdate (Froehde), vanadate (Mandeline), and selenate (Mecke) reagents are used. One of the products is a quinoline type compound (Compound I) which contains the same numbers of C, N and O atoms as morphine. The structure of Compound I shows that the N-heterocyclic ring has been opened and reformed to produce a tetracyclic almost planar structure. The oxygen of the dihydrofuran ring becomes quinonoid in ring A.

The X-ray studies of morphine sulfate and morphine methyliodide to investigate the effect on the morphine C-C skeleton change on substitution at N1 indicated that the two molecules contain similar bond angles and distances. The only difference observed is in the C-N-C average bond angle which is greater in morphine sulfate than in morphine methyliodide as expected due to the compression of the

C-N-H angle in the sulfate salt. There is no significant conformational change between these two structures.

The hydrogen bonding networks in the packing diagram of morphine sulfate and morphine methyliodide show no significant differences but both of these are different from the main hydrogen bonding network of morphine hydrate. The structural data do not differ significantly and therefore cannot be used to interpret the unique SSCD spectrum of morphine free base.

In the future the first priority in the pseudomorphine study is to obtain a suitable single crystal for a definitive X-ray study of the structure of the dimer to confirm the present tentative structural assignment. For the color reactions the remaining two products must also be isolated for characterization to support the proposed mechanism. In addition a complete ESR study needs to be done to characterize the preliminary free radical intermediates. Numerous other empirical color reactions are worthy of study including other opiates, tetracyclines, barbiturates, marijuana and cocaine. The objectives would be to evaluate their specificity and to use the information to develop other better screening reagents.

The field of solid state CD is new and combined with X-ray diffraction, could be extremely important in understanding the crystal forces which are responsible for bulk chirality, and contribute to the knowledge of solid state physics in the interpretation and development of polarizing

materials. A related compound of immediate interest is heroin (3,6-diacetylmorphine) whose SSCD is entirely negative (31). Hydrogen bonding between the heroin molecules without involving the anion or water of crystallization would be consistent with the structural data in morphine free base and would confirm the importance of direct bonding on the SSCD spectra.

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APPENDICES

APPENDIX A

X-RAY DATA OF MORPHINE SULFATE

	0.0.L	
4	845	934
6	366	300
8	970	921
10	923	908
12	397	389
14	712	699
16	76	120
18	504	486
20	49	58

	0.1.L	
1	346	290
2	1403	1407
3	660	666
4	308	339
5	11	52
7	1691	1671
9	656	697
10	31	47
11	105	140
12	38	84
13	877	861
15	274	305
16	29	49
17	103	120
18	29	55
19	326	372
20	36	80

	0.2.L	
0	997	1006
1	1370	1357
2	230	214
3	83	89
4	754	769
5	473	478
6	352	330
7	323	301
8	647	632
9	14	19
10	34	61
11	448	427
12	147	173
13	196	243
14	339	346
15	25	123
16	23	59
17	138	172
18	20	25
19	40	61
20	20	9

	0.3.L	
1	270	281
2	225	241
3	49	47
4	288	281
5	647	647
6	776	767
7	480	502
8	232	242
9	341	302
10	442	444
11	98	129
12	100	95
13	87	57
14	393	392
15	76	86
16	62	58
17	103	99
18	16	30
19	192	168
20	127	148

	0.4.L	
0	114	117
1	297	314
2	205	200
3	78	69
4	384	393
5	156	136
6	14	20
7	58	59
8	250	248
9	45	4
10	129	122
11	185	185
12	103	107
13	71	71
14	172	179
15	123	110
16	232	197
17	40	59
18	94	95
19	60	45
20	65	67

	0.5.L	
1	183	183
2	107	99
3	69	70
4	47	59
5	319	298
6	45	38
7	15	36
8	167	159
9	62	75
10	141	156
11	223	224
12	45	52
13	120	126
14	205	223
15	145	120
16	62	38
17	16	28
18	154	130
19	136	121
20	71	84

	0.6.L	
0	103	109
1	25	43
2	129	141
3	62	73
4	248	246
5	54	40
6	134	134
7	116	109
8	125	142
9	29	38
10	87	85
11	192	189
12	187	198
13	16	2
14	114	92
15	176	198
16	18	28
17	71	71
18	118	126
19	38	20
20	136	127

	0.7.L	
1	141	137
2	196	186
3	94	107
4	60	49
5	25	33
6	60	33
7	69	73
8	52	22
9	167	174
10	45	34
11	114	116
12	27	4
13	107	103
14	18	36
15	138	139
16	52	35
17	103	92
18	18	33
19	56	42
20	18	23

	0.8.L	
0	212	208
1	18	35
2	18	10
3	94	84
4	40	58
5	38	45
6	60	46
7	31	40
8	120	117
9	118	120
10	45	13
11	36	22
12	18	20
13	43	3
14	94	85
15	52	7
16	36	4
17	52	48
18	29	40
19	43	36
20	38	11

	0.9.L	
1	49	15
2	18	13
3	45	40
4	34	46
5	35	75
6	80	69
7	89	93
8	43	28
9	43	28
10	58	64
11	18	1
12	20	3
13	56	34
14	20	36
15	89	71
16	74	67
17	40	2
18	52	37
19	20	6
20	63	31

0.10.L

0	20	21
1	40	35
2	43	23
3	38	9
4	85	80
5	47	45
6	20	18
7	20	27
8	20	15
9	69	63
10	40	19
11	45	5
12	65	34
13	63	7
14	87	68
15	47	33
16	20	24
17	65	31
18	20	3
19	60	44
20	43	6

0.11.L

1	23	24
2	78	45
3	20	8
4	20	1
5	20	10
6	20	18
7	58	55
8	74	26
9	20	8
10	20	8
11	43	17
12	40	18
13	56	36
14	56	5
15	20	3
16	43	34
17	20	14
18	23	0
19	58	28
20	23	5

0.12.L

0	29	15
1	29	4
2	78	10
3	27	19
4	27	30
5	25	5
6	47	11
7	25	7
8	25	3
9	49	10
10	49	20
11	45	6
12	25	7
13	25	11
14	25	11
15	65	13
16	25	23
17	25	9
18	23	19
19	58	17
20	23	7

0.13.L

1	36	8
2	36	9
3	36	31
4	34	4
5	34	13
6	34	10
7	34	3
8	34	17
9	34	3
10	34	6
11	56	17
12	31	14
13	31	14
14	31	10
15	31	7
16	31	14
17	45	1
18	31	16
19	31	3
20	31	1

0.14.L

0	45	2
1	45	9
2	45	1
3	43	2
4	63	10
5	43	2
6	43	11
7	43	3
8	43	1
9	40	0
10	52	4
11	40	7
13	40	0
14	40	0
15	38	8
16	40	1
17	40	3
18	38	13
19	38	6

1.0.-

0	513	584
1	47	111
2	243	274
3	877	925
4	957	908
5	20	75
6	152	134
7	203	164
8	132	119
9	562	530
10	460	444
11	642	624
12	578	581
13	219	216
14	49	56
15	234	225
16	125	118
17	143	123
18	207	192
19	125	137
20	36	36

1.1.L

0	105	82
1	406	417
2	524	519
3	366	358
4	1220	1213
5	531	527
6	660	678
7	506	468
8	283	289
9	319	293
10	80	68
11	288	288
12	475	467
13	361	366
14	279	272
15	56	43
16	335	318
17	341	323
18	181	185
19	332	358
20	274	274

1.2.L

0	118	112
1	526	519
2	413	442
3	127	116
4	279	284
5	379	361
6	147	149
7	500	481
8	230	203
9	268	249
10	558	550
11	531	525
12	216	198
13	248	250
14	428	424
15	228	224
16	65	54
17	214	205
18	67	44
19	89	92
20	310	309

1.3.L

0	65	68
1	170	192
2	216	218
3	393	410
4	147	138
5	502	507
6	241	231
7	417	409
8	174	173
9	259	242
10	207	201
11	125	100
12	127	134
13	87	78
14	125	133
15	49	34
16	112	117
17	98	69
18	141	157
19	94	92
20	52	80

1.4.L

0	185	175
1	125	116
2	228	219
3	62	50
4	120	122

	1,4,L	
5	154	134
6	315	314
7	76	80
8	250	262
9	62	66
10	118	103
11	78	93
12	125	136
13	47	51
14	49	28
15	123	131
16	65	75
17	85	84
18	141	145
19	129	121
20	181	162

	1,5,L	
0	248	246
1	107	79
2	216	214
3	56	49
4	127	133
5	143	145
6	281	272
7	89	81
8	223	219
9	252	249
10	56	50
11	89	83
12	190	191
13	89	84
14	89	91
15	89	101
16	152	158
17	132	139
18	62	72
19	127	115
20	16	49

	1,6,L	
0	114	102
1	123	113
2	125	146
3	127	124
4	45	65
5	134	132
6	47	45
7	170	167
8	112	108
9	96	83
10	145	144
11	161	158
12	91	87
13	96	91
14	85	84
15	216	209
16	143	130
17	76	73
18	31	38
19	115	105
20	27	31

	1,7,L	
0	60	55
1	85	73
2	94	94
3	80	92
4	67	72
5	129	122
6	125	125
7	63	71
8	89	92
9	56	51
10	87	70
11	71	82
12	80	76
13	78	84
14	18	20
15	52	28
16	49	28
17	43	23
18	89	99
19	49	43
20	63	64

	1,8,L	
0	18	29
1	103	101
2	67	57
3	105	96
4	58	64
5	36	44
6	38	11
7	18	3
8	18	35
9	112	107
10	60	60
11	109	99
12	40	65
13	49	51
14	63	52
15	63	51
16	67	67
17	65	48
18	67	64
19	58	65
20	31	24

	1,9,L	
0	18	26
1	25	26
2	49	27
3	18	28
4	49	41
5	49	30
6	52	33
7	27	37
8	78	67
9	63	51
10	112	99
11	85	72
12	56	37
13	29	15
14	58	29
15	54	35
16	78	65
17	72	48
18	87	88
19	20	39
20	69	57

	1,10,L	
0	58	15
1	36	36
2	56	31
3	20	30
4	20	12
5	56	41
6	49	29
7	20	26
8	60	36
9	45	52
10	20	32
11	23	45
12	40	19
13	20	25
14	20	3
15	47	33
16	20	31
17	67	33
18	31	10
19	60	51
20	58	31

	1,11,L	
0	54	12
1	23	16
2	23	35
3	72	22
4	40	37
5	56	22
6	23	11
7	23	13
8	43	17
9	23	14
10	34	31
11	31	17
12	20	24
13	23	7
14	45	28
15	20	24
16	20	42
17	23	36
18	49	11
19	20	17
20	23	15

	1,12,L	
0	29	12
1	29	3
2	29	15
3	29	19
4	29	8
5	29	17
6	60	16
7	27	30
8	40	27
9	27	17
10	45	4
11	27	1
12	63	15
13	40	9
14	47	11
15	27	13
16	25	10
17	25	15
18	38	11
19	25	11
20	25	24

	1,13,L	
0	38	26
1	38	20
2	38	19
3	94	12
4	38	1
5	36	9

1.13.L

5	36	15
7	36	15
8	36	8
9	52	10
10	54	7
11	34	6
12	49	18
13	65	6
14	34	16
15	34	6
16	52	10
17	31	7
18	34	14
19	31	8
20	31	3

1.14.L

0	47	1
1	47	9
2	94	4
3	45	9
4	45	4
5	45	6
6	45	8
7	92	9
8	43	6
9	94	7
10	43	7
11	43	6
12	43	5
14	43	7
15	40	7
16	58	7
17	40	5
18	40	4
19	40	9

2.0.L

0	194	228
1	185	191
2	591	547
3	585	579
4	172	173
5	214	260
6	335	348
7	25	53
8	716	687
9	232	209
10	348	354
11	290	270
12	547	553
13	286	274
14	47	48
15	45	68
16	201	221
17	14	18
18	245	239
19	194	195
20	60	68

2.1.L

0	395	413
1	219	212
2	515	531
3	355	340
4	683	660
5	332	315
6	616	619
7	192	171
8	165	187
9	404	394
10	319	299
11	132	146
12	91	94
13	346	343
14	223	227
15	85	80
16	165	159
17	344	353
18	116	118
19	136	152
20	161	167

2.2.L

0	1026	1004
1	564	550
2	194	202
3	364	352
4	315	309
5	341	337
6	346	346
7	348	355
8	241	231
9	384	377
10	149	154
11	136	117
12	147	139
13	187	181
14	274	261
15	270	265
16	187	197
17	196	210
18	143	146
19	52	44
20	107	99

2.3.L

0	225	234
1	112	107
2	337	344
3	154	160
4	34	32
5	147	143
6	207	229
7	143	129
8	163	170
9	123	124
10	239	257
11	232	237
12	65	61
13	216	222
14	161	157
15	80	79
16	210	209
17	216	224
18	243	243
19	56	58
20	149	154

2.4.L

0	145	152
1	234	240
2	78	65
3	219	221
4	210	208
5	214	196
6	45	46
7	210	215
8	241	250
9	395	401
10	74	66
11	344	342
12	116	101
13	141	144
14	47	65
15	136	144
16	187	189
17	337	340
18	83	92
19	183	169
20	47	71

2.5.L

0	80	73
1	85	88
2	292	301
3	52	16
4	134	129
5	154	161
6	138	141
7	62	51
8	154	150
9	212	201
10	223	213
11	127	128
12	147	149
13	87	92
14	170	172
15	45	40
16	214	204
17	40	36
18	98	87
19	147	143
20	156	160

2.6.L

0	52	58
1	118	116
2	78	99
3	76	80
4	98	94
5	163	162
6	118	99
7	74	64
8	94	94
9	78	74
10	65	62
11	56	40
12	196	194
13	112	107
14	65	76
15	74	71
16	78	86
17	54	56
18	154	160
19	36	4
20	34	22

2.7.L

0	49	42
1	103	109
2	105	105
3	96	86
4	107	108
5	94	90
6	18	30
7	45	31
8	43	42

2.7.L

9	98	92
10	69	66
11	58	60
12	67	72
13	60	42
14	58	57
15	107	100
16	58	74
17	65	77
18	18	16
19	18	31
20	54	39

2.8.L

0	13	18
1	56	35
2	31	18
3	65	57
4	31	17
5	103	98
6	65	53
7	58	48
8	45	45
9	18	34
10	76	54
11	38	51
12	45	59
13	127	115
14	45	43
15	60	70
16	60	45
17	31	14
18	40	50
19	69	68
20	80	77

2.9.L

0	18	21
1	58	59
2	36	47
3	16	18
4	58	48
5	52	61
6	83	82
7	31	8
8	69	54
9	19	23
10	58	42
11	69	48
12	71	50
13	20	9
14	80	67
15	20	28
16	20	31
17	38	11
18	65	64
19	20	20
20	34	37

2.10.L

0	20	19
1	72	37
2	52	43
3	45	47
4	20	30
5	54	26
6	20	10
7	38	23
8	20	16
9	94	51
10	20	8
11	20	16
12	20	21
13	56	51
14	65	34
15	20	39
16	20	18
17	36	25
18	52	25
19	20	31
20	38	24

2.11.L

0	56	47
1	23	21
2	47	14
3	23	5
4	23	14
5	23	18
6	23	38
7	36	4
8	23	38
9	69	11
10	23	32
11	23	17
12	47	25
13	23	9
14	23	11
15	20	9
16	23	23
17	23	27
18	47	28
19	20	10
20	23	47

2.12.L

0	29	12
1	52	23
2	29	7
3	72	19
4	25	11
5	29	11
6	29	16
7	54	6
8	29	30
9	29	22
10	27	9
11	27	18
12	27	21
13	27	12
14	27	4
15	58	9
16	27	12
17	27	19
18	43	20
19	25	8
20	25	21

2.13.L

0	38	9
1	85	18
2	38	17
3	38	9
4	38	16
5	38	17
6	38	22
7	38	11
8	72	10
9	83	10
10	36	14
11	36	6
12	36	4
13	36	8
14	67	5
15	34	10
16	34	12
17	34	3
18	34	13
19	65	9
20	31	5

2.14.L

0	45	7
2	47	3
3	45	11
4	98	13
5	45	3
6	45	11
8	45	5
9	45	6
10	45	7
11	45	5
12	43	4
13	43	12
15	43	7
16	43	3
18	40	5

3.0.L

0	303	307
1	29	11
2	415	394
3	43	15
4	11	18
5	47	57
6	366	377
7	395	384
8	495	501
9	292	306
10	167	177
11	270	264
12	43	46
13	502	475
14	453	452
15	192	194
16	265	273
17	120	115
18	76	67
19	29	7
20	47	48

3.1.L

0	299	308
1	170	153
2	154	170
3	225	234
4	172	162
5	308	305
6	254	238
7	370	368
8	49	54
9	134	143
10	181	165
11	62	33
12	288	280
13	326	326
14	196	197
15	199	212

3.1.L

16	270	270
17	239	233
18	71	63
19	112	125
20	223	223

3.2.L

0	265	257
1	460	473
2	604	603
3	178	176
4	292	277
5	172	149
6	321	321
7	125	122
8	303	302
9	125	134
10	158	140
11	78	74
12	263	272
13	236	237
14	201	187
15	114	106
16	60	44
17	85	73
18	248	256
19	23	31
20	52	42

3.3.L

0	25	29
1	145	144
2	65	63
3	326	325
4	263	267
5	310	294
6	468	470
7	265	278
8	170	160
9	158	173
10	123	110
11	350	357
12	158	170
13	299	320
14	52	54
15	272	261
16	147	161
17	116	121
18	78	80
19	76	82
20	83	97

3.4.L

0	161	160
1	257	252
2	178	175
3	56	38
4	71	60
5	83	67
6	265	267
7	143	140
8	196	201
9	129	143
10	94	96
11	109	122
12	214	224
13	330	328
14	263	273
15	207	200
16	165	163
17	221	222
18	152	158
19	120	110
20	107	129

3.5.L

0	43	18
1	156	152
2	196	197
3	230	235
4	96	82
5	80	59
6	134	121
7	223	203
8	76	76
9	52	13
10	16	23
11	158	149
12	187	184
13	156	149
14	143	143
15	212	223
16	16	21
17	145	128
18	16	23
19	63	71
20	129	127

3.6.L

0	16	19
1	141	139
2	199	190
3	36	49
4	74	61
5	185	182
6	125	117
7	52	46
8	165	159
9	16	35
10	107	105
11	78	63
12	56	53
13	65	54
14	76	70
15	65	66
16	38	37
17	18	24
18	120	114
19	18	16
20	67	61

3.7.L

0	38	33
1	127	132
2	67	58
3	18	17
4	43	33
5	18	43
6	109	97
7	85	78
8	49	34
9	74	77
10	52	24
11	71	63
12	18	27
13	76	66
14	18	22
15	47	32
16	63	52
17	98	110
18	52	16
19	31	33
20	91	85

3.8.L

0	34	33
1	34	40
2	89	62
3	114	98
4	31	27
5	65	56
6	71	42
7	18	27
8	74	71
9	18	35
10	36	59
11	40	25
12	34	14
13	18	32
14	18	28
15	83	63
16	18	13
17	18	22
18	18	33
19	18	11
20	58	61

3.9.L

0	65	33
1	65	67
2	52	46
3	69	42
4	43	23
5	56	48
6	18	13
7	63	33
8	20	19
9	38	41
10	18	23
11	58	47
12	34	29
13	40	34
14	18	11
15	20	26
16	20	16
17	63	45
18	20	32
19	60	45
20	20	16

3.10.L

0	54	41
1	20	4
2	87	70
3	20	6
4	67	32
5	40	27
6	20	30
7	52	28
8	45	15
9	20	19
10	31	45
11	20	13
12	45	31
13	56	20
14	20	9
15	47	21
16	40	33

3,10,L

17	20	7
18	20	39
19	20	8
20	20	27

3,11,L

0	23	34
1	23	4
2	31	17
3	23	31
4	23	35
5	23	23
6	23	15
7	56	25
8	40	23
9	23	40
10	23	6
11	45	28
12	23	14
13	38	15
14	58	22
15	23	19
16	36	16
17	54	16
18	43	17
19	23	18
20	23	24

3,12,L

0	29	17
1	29	4
2	67	13
3	29	11
4	40	19
5	72	20
6	29	16
7	29	11
8	63	9
9	47	12
10	29	16
11	27	4
12	65	20
13	27	13
14	67	14
15	27	6
16	27	17
17	27	15
18	25	14
19	25	4
20	25	3

3,13,L

0	78	10
1	38	5
2	38	7
3	38	14
4	38	6
5	60	18
6	38	9
7	38	15
8	38	7
9	36	10
10	38	7
11	36	4
12	36	6
13	36	7
14	63	11
15	36	8
16	36	5
17	36	11
18	34	4
19	34	11
20	34	5

3,14,L

1	45	7
2	78	8
3	89	7
4	45	11
6	45	2
7	45	3
8	45	8
9	85	6
10	45	6
11	74	1
13	43	4
14	43	6
15	43	1
16	43	6

4,0,L

0	263	256
1	460	461
2	214	208
3	125	117
4	58	74
5	29	40
6	129	107
7	243	247
8	386	376
9	274	257
10	277	279
11	96	78
12	51	71
13	58	42
14	154	162
15	250	246
16	192	213
17	263	257
18	45	3
19	80	50
20	16	41

4,1,L

0	109	89
1	145	167
2	522	524
3	263	258
4	448	435
5	301	305
6	62	44
7	230	224
8	219	218
9	74	82
10	165	151
11	170	152
12	205	219
13	207	215
14	165	183
15	107	93
16	80	76
17	149	140
18	78	86
19	196	190
20	205	219

4,2,L

0	158	182
1	261	257
2	448	463
3	216	197
4	236	238
5	163	144
6	196	183
7	393	406
8	187	193
9	451	466
10	136	143
11	212	198
12	381	391
13	141	143
14	118	110
15	96	109
16	203	201
17	156	149
18	203	224
19	54	30
20	31	36

4,3,L

0	221	218
1	154	173
2	236	223
3	337	354
4	34	6
5	310	315
6	65	68
7	239	233
8	65	28
9	274	282
10	123	127
11	181	161
12	116	119
13	116	115
14	174	167
15	181	177
16	172	176
17	138	136
18	16	24
19	234	224
20	56	18

4,4,L

0	132	124
1	158	149
2	203	203
3	181	175
4	190	178
5	187	186
6	170	170
7	125	123
8	145	144
9	161	165
10	118	119
11	98	95
12	381	376
13	312	300
14	154	136
15	143	131
16	149	150
17	71	62
18	47	18
19	69	71
20	18	7

4,5,L

0	52	47

4,5,L

1	172	187
2	118	124
3	221	235
4	80	70
5	185	177
6	174	177
7	243	243
8	134	138
9	60	64
10	87	95
11	116	111
12	100	117
13	56	48
14	76	86
15	36	45
16	65	56
17	94	94
18	16	28
19	136	129
20	36	49

4,6,L

0	60	75
1	109	105
2	105	103
3	40	34
4	78	83
5	67	59
6	89	86
7	56	45
8	78	69
9	91	82
10	85	72
11	34	47
12	96	67
13	112	106
14	76	63
15	65	64
16	109	115
17	25	14
18	52	42
19	34	40
20	52	52

4,7,L

0	34	3
1	43	37
2	60	53
3	38	40
4	49	18
5	18	21
6	105	104
7	94	88
8	40	22
9	85	71
10	18	23
11	56	42
12	56	64
13	18	5
14	56	40
15	58	27
16	18	22
17	65	63
18	45	7
19	89	65
20	76	75

4,8,L

0	100	94
1	18	17
2	49	49
3	69	82
4	18	12
5	74	54
6	20	29
7	36	31
8	94	70
9	36	54
10	56	49
11	29	37
12	36	30
13	20	31
14	20	26
15	27	39
16	43	54
17	43	39
18	40	38
19	20	8
20	20	54

4,9,L

0	67	48
1	74	77
2	69	37
3	18	16
4	20	16
5	63	57
6	20	19
7	49	48
8	20	35
9	80	70
10	47	34
11	20	34
12	20	14
13	20	26
14	20	1
15	20	40
16	29	30
17	20	12
18	67	40
19	52	29
20	36	20

4,10,L

0	20	28
1	47	21
2	56	38
3	63	29
4	20	8
5	38	24
6	52	47
7	36	47
8	20	38
9	38	24
10	20	5
11	49	3
12	45	30
13	20	15
14	20	6
15	38	24
16	63	38
17	38	21
18	23	25
19	49	4
20	36	25

4,11,L

0	47	12
1	23	18
2	23	24
3	40	7
4	47	41
5	60	16
6	23	2
7	40	17
8	23	14
9	78	9
10	23	11
11	23	15
12	23	20
13	56	24
14	56	38
15	23	24
16	47	30
17	23	8
18	23	14
19	23	9
20	23	10

4,12,L

0	58	8
1	29	4
2	29	17
3	29	4
4	29	14
5	76	28
6	29	17
7	29	19
8	29	10
9	29	12
10	29	9
11	60	10
12	29	13
13	29	15
14	27	9
15	27	13
16	65	4
17	27	7
18	43	8
19	52	5
20	27	12

4,13,L

0	38	14
2	38	18
3	38	9
4	65	6
5	38	8
6	38	6
7	38	6
8	38	6
10	38	4
11	38	11
12	36	6
13	36	8
14	36	10
15	36	6
16	36	2
17	36	11
18	56	2
19	34	7
20	34	11

4,14,L

0	98	5
1	47	3
2	45	5
3	47	4

4,14,L

4	45	10
5	47	4
6	67	4
7	45	6
8	45	14
9	45	7
10	45	7
11	45	6
12	72	3
13	45	6

5,0,L

0	14	39
1	154	159
2	161	182
3	156	167
4	103	106
5	62	74
6	286	294
7	165	162
8	89	69
9	118	129
10	60	69
11	185	194
12	47	48
13	181	180
14	203	208
15	40	33
16	103	107
17	62	61
18	261	255
19	393	392
20	232	237

5,1,L

0	120	133
1	76	79
2	116	126
3	109	110
4	127	136
5	230	238
6	138	149
7	80	79
8	187	196
9	65	66
10	167	187
11	69	61
12	344	344
13	165	158
14	145	146
15	56	40
16	129	129
17	212	217
18	167	159
19	16	41
20	47	46

5,2,L

0	152	137
1	196	202
2	71	65
3	199	210
4	127	117
5	96	84
6	134	131
7	216	242
8	96	101
9	205	207
10	118	118
11	118	106
12	71	61
13	203	205
14	67	76
15	315	338
16	103	94
17	143	144
18	83	74
19	245	241
20	221	230

5,3,L

0	183	173
1	132	117
2	60	49
3	112	100
4	156	159
5	118	126
6	167	166
7	67	72
8	277	282
9	252	257
10	176	185
11	85	83
12	214	214
13	274	281
14	138	147
15	103	113
16	120	122
17	83	81
18	299	295
19	76	58
20	91	98

5,4,L

0	49	68
1	125	136
2	78	73
3	245	240
4	78	68
5	49	51
6	87	87
7	143	131
8	149	149
9	185	176
10	69	86
11	323	322
12	114	110
13	31	35
14	85	100
15	60	60
16	83	77
17	165	157
18	56	61
19	103	97
20	100	93

5,5,L

0	96	94
1	91	81
2	52	32
3	45	9
4	103	113
5	116	113
6	16	32
7	62	60
8	163	145
9	83	97
10	60	74
11	16	13
12	16	26
13	38	40
14	103	107
15	58	57
16	65	64
17	36	14
18	138	136
19	52	59
20	67	47

5,6,L

0	34	16
1	58	42
2	65	49
3	16	21
4	47	45
5	16	25
6	16	6
7	127	123
8	69	59
9	49	29
10	40	27
11	100	101
12	76	66
13	43	65
14	45	22
15	83	108
16	69	82
17	89	75
18	45	21
19	34	43
20	47	41

5,7,L

0	18	29
1	49	40
2	71	70
3	56	53
4	118	116
5	80	65
6	43	36
7	18	16
8	76	69
9	76	59
10	89	72
11	18	10
12	71	60
13	43	37
14	89	89
15	40	32
16	54	23
17	18	16
18	18	32
19	38	44
20	20	47

5,8,L

0	31	18
1	18	29
2	43	22
3	80	75
4	60	63
5	105	107
6	20	5
7	87	76
8	52	51
9	18	18
10	52	27
11	69	49

5,8,L

12	29	26
13	60	54
14	60	19
15	20	32
16	20	4
17	47	38
18	20	23
19	40	49
20	58	45

5,9,L

0	20	26
1	38	29
2	20	27
3	20	34
4	31	59
5	49	49
6	67	55
7	45	42
8	29	22
9	20	32
10	20	13
11	38	11
12	49	54
13	31	23
14	56	59
15	20	11
16	20	29
17	18	20
18	47	28
19	34	14
20	20	20

5,10,L

0	20	12
1	20	18
2	20	4
3	20	42
4	20	13
5	20	19
6	20	32
7	52	18
8	20	19
9	23	30
10	43	12
11	31	8
12	76	45
13	43	6
14	23	1
15	52	38
16	69	54
17	31	20
18	45	30
19	23	22
20	54	22

5,11,L

0	25	30
1	23	20
2	43	11
3	43	17
4	23	3
5	23	19
6	52	19
7	36	14
8	60	23
9	43	26
10	56	25
11	23	7
12	47	24
13	43	24
14	23	18
15	23	7
16	23	15
17	23	10
18	23	23
19	23	10
20	23	18

5,12,L

0	29	15
1	29	18
2	29	25
3	29	15
4	81	10
5	83	8
6	29	11
7	29	6
8	29	4
9	29	12
10	29	8
11	29	16
12	65	5
13	29	9
14	29	14
15	29	14
16	72	4
17	27	6
18	56	10
19	69	9
20	27	9

5,13,L

0	38	3
1	85	1
2	38	19
3	38	7
4	38	12
5	58	0
6	38	18
7	38	10
8	38	12
9	38	5
10	38	4
11	81	5
12	38	2
13	36	6
14	60	3
15	36	3
16	36	10
17	36	4
18	36	5
19	65	7
20	34	7

5,14,L

0	45	1
1	45	9
2	45	4
3	45	2
4	45	6
5	65	4
6	45	7
7	45	9

6,0,L

0	350	357
1	49	7
2	85	90
3	69	52
4	277	281
5	299	312
6	214	241
7	207	217
8	125	116
9	100	96
10	91	81
11	40	13
12	98	101
13	248	236
14	129	143
15	127	126
16	181	177
17	31	19
18	96	106
19	29	30
20	23	31

6,1,L

0	127	130
1	145	148
2	268	275
3	62	51
4	40	50
5	74	81
6	27	25
7	67	75
8	161	168
9	80	65
10	123	106
11	152	152
12	234	225
13	190	181
14	286	296
15	167	171
16	138	129
17	100	107
18	38	18
19	47	72
20	196	193

6,2,L

0	60	52
1	145	156
2	54	32
3	74	46
4	230	240
5	62	62
6	103	108
7	112	115
8	120	116
9	69	68
10	167	172
11	129	138
12	100	82
13	125	134
14	56	55
15	158	159
16	71	49
17	65	52
18	216	200
19	112	94
20	78	81

6,3,L

0	74	65
1	156	168

6,3,L

2	91	103
3	214	206
4	80	60
5	38	40
6	54	52
7	129	124
8	100	107
9	149	162
10	78	59
11	239	245
12	112	130
13	132	130
14	118	113
15	165	190
16	145	142
17	100	93
18	89	70
19	67	78
20	58	64

6,4,L

0	277	294
1	58	62
2	85	73
3	67	62
4	112	110
5	69	80
6	125	119
7	105	103
8	120	120
9	89	88
10	16	7
11	67	84
12	67	68
13	49	52
14	174	172
15	63	74
16	78	82
17	105	84
18	18	38
19	18	5
20	18	38

6,5,L

0	40	50
1	45	51
2	136	134
3	58	32
4	25	15
5	47	36
6	89	79
7	107	105
8	25	34
9	47	17
10	47	41
11	71	72
12	18	37
13	25	45
14	76	71
15	87	80
16	18	16
17	58	55
18	49	52
19	71	40
20	38	16

6,6,L

0	54	53
1	67	60
2	18	2
3	120	105
4	118	93
5	38	17
6	36	22
7	52	36
8	56	61
9	47	25
10	105	91
11	112	108
12	39	37
13	100	93
14	52	40
15	125	112
16	49	40
17	56	40
18	76	72
19	34	36
20	43	19

6,7,L

0	18	32
1	45	58
2	63	18
3	31	39
4	60	56
5	63	72
6	100	89
7	85	66
8	96	85
9	65	52
10	34	42
11	58	64
12	20	28
13	98	81
14	18	21
15	60	51
16	31	46
17	54	22
18	58	24
19	18	16
20	20	26

6,8,L

0	29	21
1	56	64
2	34	18
3	20	21
4	118	113
5	40	30
6	20	39
7	56	51
8	74	33
9	20	36
10	76	42
11	54	36
12	31	28
13	63	31
14	60	32
15	20	15
16	58	33
17	31	20
18	49	28
19	20	17
20	40	16

6,9,L

0	45	27
1	20	45
2	38	32
3	69	65
4	49	20
5	20	32
6	47	34
7	38	23
8	47	42
9	69	36
10	20	22
11	65	65
12	38	12
13	20	21
14	20	9
15	20	13
16	34	16
17	56	26
18	20	23
19	23	35
20	31	43

6,10,L

0	58	30
1	20	24
2	20	11
3	20	32
4	36	18
5	31	17
6	20	23
7	20	13
8	20	23
9	20	10
10	40	26
11	23	17
12	69	45
13	20	14
14	20	3
15	45	13
16	20	29
17	34	7
18	47	43
19	45	18
20	45	16

6,11,L

0	23	1
1	38	3
2	47	16
3	23	24
4	23	12
5	49	23
6	23	5
7	23	2
8	23	9
9	25	27
10	23	13
11	38	19
12	23	3
13	43	14
14	23	14
15	54	12
16	47	17
17	38	17
18	23	8
19	23	8
20	23	8

6,12,L

0	94	19
1	29	10
2	31	23

6,12,L

3	29	1
4	67	3
5	29	12
6	29	9
7	29	6
8	29	10
9	29	10
10	29	6
11	29	5
12	29	8
13	27	3
14	67	11
15	29	3
16	27	8
17	27	10
18	29	6
19	27	4
20	78	4

6,13,L

0	38	1
1	38	10
2	38	10
3	38	5
4	38	8
5	38	5
6	38	4
7	38	15
8	38	4
9	38	13
10	36	2
11	56	2
12	36	10
13	36	6
14	36	5
15	36	2
16	36	2
17	36	10
18	36	9
19	62	15
20	34	3

7,0,L

0	292	299
1	71	71
2	178	173
3	158	151
4	303	325
5	216	221
6	187	198
7	178	182
8	259	256
9	40	1
10	134	134
11	27	8
12	145	143
13	181	181
14	103	88
15	134	134
16	152	138
17	65	33
18	178	151
19	152	139
20	152	130

7,1,L

0	317	320
1	167	164
2	279	280
3	123	131
4	54	32
5	125	119
6	199	203
7	103	100
8	105	98
9	377	393
10	67	63
11	83	57
12	85	80
13	141	135
14	161	160
15	109	112
16	78	72
17	141	143
18	114	102
19	129	110
20	74	60

7,2,L

0	87	100
1	114	122
2	167	161
3	96	87
4	223	236
5	225	239
6	183	191
7	252	267
8	145	154
9	127	127
10	118	115
11	152	144
12	185	181
13	107	84
14	107	95
15	91	91
16	116	116
17	18	20
18	18	26
19	65	53
20	85	88

7,3,L

0	134	148
1	109	96
2	76	63
3	78	88
4	78	64
5	145	170
6	98	94
7	116	97
8	118	137
9	49	18
10	152	154
11	52	59
12	114	100
13	199	188
14	105	85
15	67	71
16	18	28
17	18	43
18	18	13
19	67	48
20	58	30

7,4,L

0	27	36
1	56	68
2	98	85
3	149	145
4	85	91
5	67	65
6	34	41
7	18	34
8	89	87
9	71	57
10	116	120
11	107	68
12	83	66
13	60	57
14	74	75
15	58	59
16	105	110
17	38	17
18	54	43
19	54	37
20	63	63

7,5,L

0	94	75
1	69	75
2	18	23
3	69	62
4	65	58
5	105	95
6	63	56
7	69	57
8	18	23
9	67	63
10	80	75
11	78	73
12	18	23
13	143	129
14	85	88
15	43	28
16	34	17
17	18	41
18	74	61
19	18	26
20	63	45

7,6,L

0	38	44
1	56	48
2	18	38
3	54	29
4	87	81
5	31	50
6	114	107
7	83	75
8	80	40
9	18	18
10	89	59
11	109	110
12	60	50
13	18	19
14	74	68
15	18	47
16	65	70
17	18	20
18	58	24
19	43	37
20	89	88

7,7,L

0	31	29
1	98	79
2	83	61
3	80	79

7.7.L

4	43	26
5	40	16
6	38	51
7	56	46
8	40	11
9	125	111
10	74	39
11	40	39
12	20	21
13	31	28
14	38	15
15	36	37
16	20	28
17	100	70
18	43	38
19	20	7
20	20	25

7.8.L

0	91	89
1	20	16
2	43	51
3	20	35
4	31	52
5	65	42
6	76	66
7	69	56
8	63	57
9	20	13
10	20	21
11	38	11
12	47	26
13	65	34
14	40	25
15	58	24
16	63	38
17	20	18
18	38	32
19	34	25
20	67	44

7.9.L

0	20	52
1	34	16
2	40	37
3	49	27
4	20	13
5	56	59
6	20	22
7	20	19
8	66	20
9	49	25
10	63	15
11	65	41
12	58	15
13	38	40
14	76	28
15	47	33
16	20	14
17	20	10
18	20	23
19	20	10
20	52	30

7.10.L

0	20	26
1	20	14
2	20	31
3	20	10
4	23	37
5	49	22
6	23	20
7	20	24
8	20	13
9	20	13
10	45	1
11	36	5
12	69	30
13	23	6
14	23	19
15	20	15
16	36	20
17	20	6
18	23	14
19	23	11
20	23	8

7.11.L

0	23	7
1	25	18
2	45	9
3	63	5
4	49	5
5	43	24
6	23	2
7	25	16
8	25	2
9	25	11
10	25	7
11	36	4
12	60	9
13	23	19
14	49	16
15	23	3
16	52	4
17	23	7
18	45	5
19	23	20
20	23	9

7.12.L

0	29	4
1	29	13
2	29	14
3	29	6
4	29	10
5	54	12
6	98	6
7	29	9
8	45	8
9	29	7
10	74	9
11	29	14
12	29	12
13	29	0
14	29	6
15	29	7
16	29	16
17	29	9
18	29	4
19	27	2
20	27	3

7.13.L

0	38	8
1	38	2
2	38	4
3	38	9
4	38	12
5	38	12
6	38	1
7	38	5
8	38	5
9	38	8
10	38	1
11	38	6
12	38	4
13	36	9
14	36	7
15	36	10
16	36	5

8.0.L

0	16	29
1	69	53
2	47	46
3	143	145
4	34	15
5	152	151
6	89	68
7	74	92
8	54	42
9	120	122
10	83	69
11	58	48
12	76	76
13	31	35
14	63	65
15	69	65
16	45	38
17	109	105
18	38	40
19	29	7
20	18	30

8.1.L

0	38	15
1	40	13
2	125	128
3	65	40
4	87	88
5	91	87
6	181	163
7	105	97
8	45	29
9	67	53
10	129	120
11	60	35
12	96	79
13	40	44
14	43	57
15	36	30
16	80	77
17	54	40
18	34	24
19	67	72
20	49	20

8.2.L

0	85	80
1	71	81
2	18	37
3	67	69
4	38	45
5	114	111
6	69	89
7	63	54
8	80	84

8,2,L

9	62	64
10	52	45
11	36	37
12	18	14
13	63	75
14	69	70
15	67	60
16	27	9
17	18	39
18	18	17
19	18	16
20	49	18

8,3,L

0	40	53
1	100	96
2	83	83
3	31	24
4	74	78
5	18	23
6	18	35
7	18	23
8	18	19
9	31	46
10	116	105
11	52	44
12	45	40
13	69	59
14	18	27
15	96	79
16	29	35
17	18	9
18	29	39
19	56	26
20	63	55

8,4,L

0	18	2
1	34	38
2	47	45
3	47	44
4	67	60
5	107	91
6	38	37
7	103	92
8	18	35
9	56	41
10	45	18
11	69	60
12	45	39
13	18	20
14	18	34
15	18	6
16	34	22
17	76	60
18	54	58
19	54	36
20	49	15

8,5,L

0	65	68
1	52	30
2	49	58
3	67	64
4	67	63
5	43	34
6	49	28
7	36	34
8	27	19
9	69	78
10	69	63
11	78	82
12	45	40
13	34	29
14	100	96
15	60	13
16	38	28
17	20	36
18	63	24
19	40	44
20	54	33

8,6,L

0	83	80
1	49	21
2	45	15
3	118	100
4	27	21
5	96	86
6	18	12
7	83	87
8	20	27
9	47	43
10	63	45
11	20	38
12	49	19
13	36	34
14	18	19
15	20	21
16	18	21
17	65	43
18	58	57
19	52	8
20	20	21

8,7,L

0	69	75
1	43	30
2	89	73
3	18	25
4	36	45
5	31	28
6	20	29
7	54	33
8	34	34
9	69	30
10	98	70
11	52	24
12	67	43
13	31	11
14	63	53
15	20	28
16	20	38
17	20	1
18	49	32
19	38	20
20	43	49

8,8,L

0	20	13
1	47	34
2	20	40
3	20	28
4	38	26
5	38	20
6	29	17
7	20	30
8	56	21
9	76	63
10	20	7
11	56	37
12	49	29
13	60	25
14	20	19
15	23	36
16	36	33
17	87	75
18	20	15
19	23	35
20	43	46

8,9,L

0	20	26
1	20	7
2	20	37
3	45	12
4	20	15
5	20	27
6	20	27
7	20	16
8	20	30
9	20	24
10	31	42
11	31	28
12	23	17
13	20	17
14	20	7
15	49	34
16	23	21
17	20	10
18	20	18
19	54	11
20	36	18

8,10,L

0	34	4
1	49	20
2	47	26
3	20	10
4	23	13
5	20	10
6	23	9
7	20	18
8	20	9
9	23	12
10	45	2
11	20	16
12	23	16
13	43	16
14	23	11
15	23	13
16	38	24
17	63	9
18	20	13
19	52	20
20	23	11

8,11,L

0	49	1
1	56	6
2	23	10
3	23	12
4	25	11
5	47	15
6	23	14
7	23	7
8	23	10
9	23	11

8.11.L

10	56	10
11	23	13
12	23	9
13	23	6
14	23	6
15	23	7
16	23	16
17	23	9
18	23	4
19	23	16
20	23	10

8.12.L

0	25	1
1	29	10
2	29	5
3	54	7
4	29	3
5	25	8
6	29	8
7	29	8
8	25	7
9	29	6
10	29	5
11	49	4
12	29	8
13	29	13
14	76	4
15	72	16
16	29	11
17	29	2
18	27	8
19	45	5
20	65	13

8.13.L

0	38	8
1	38	6
2	38	5
3	38	3
4	38	2
5	38	7
6	38	12
7	85	7
8	38	6
9	69	5

9.0.L

0	149	159
1	109	94
2	69	57
3	69	49
4	38	5
5	147	148
6	112	95
7	87	90
8	103	111
9	78	83
10	18	10
11	18	43
12	34	13
13	94	97
14	87	73
15	112	87
16	31	5
17	34	36
18	18	46
19	18	16
20	38	5

9.1.L

0	63	60
1	94	84
2	85	85
3	83	71
4	96	82
5	54	37
6	116	108
7	43	42
8	65	41
9	18	41
10	45	42
11	65	64
12	85	84
13	18	23
14	78	68
15	31	40
16	69	63
17	43	40
18	18	12
19	47	22
20	54	37

9.2.L

0	31	1
1	54	32
2	98	102
3	58	25
4	112	110
5	98	91
6	56	36
7	45	64
8	18	53
9	67	63
10	78	76
11	60	41
12	60	56
13	18	7
14	49	25
15	40	42
16	18	11
17	67	53
18	87	83
19	47	25
20	76	63

9.3.L

0	149	153
1	60	56
2	89	97
3	45	57
4	25	4
5	63	69
6	49	24
7	91	58
8	80	80
9	18	18
10	91	75
11	43	40
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9.4.L

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12	72	45
13	67	47
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17	103	99
18	60	30
19	89	66
20	20	16

9.5.L

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17	83	63
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9.6.L

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9,7,L

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9,8,L

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9,9,L

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9,10,L

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9,11,L

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9,12,L

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10,0,-

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18	38	17
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10,1,L

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10,2,L

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18	36	44
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10,3,L

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10.3.L

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16	47	22
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19	76	62
20	72	58

10.4.L

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10.5.L

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13	80	73
14	58	9
15	85	82
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20	40	22

10.6.L

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10.7.L

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10.8.L

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20	38	15

10.9.L

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20	23	12

10.10.L

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17	23	4
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20	23	9

10.11.L

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17	23	4
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10.12.L

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11,12,L

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11,3,L

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11,1,L

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11,2,L

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11,3,L

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11,4,L

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11,5,L

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11,6,L

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11,7,L

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11,8,L

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13	40	2

11.8.L

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20	23	6

11.9.L

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11.10.L

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11.11.L

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17	23	0

12.0.L

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19	69	31
20	36	30

12.1.L

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12.2.L

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12.3.L

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12.4.L

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12.5.L

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12.5.L

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12.6.L

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12.7.L

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12.8.L

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12.9.L

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12.10.L

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12.11.L

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13.0.L

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13.1.L

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13.2.L

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13.3.L

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13.3.L

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13.4.L

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13.5.L

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13.6.L

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13.7.L

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18	23	9
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20	23	3

13.8.L

0	23	9
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3	23	8
4	43	17
5	40	4
6	23	11
7	63	19
8	23	8
9	49	1
10	52	5
11	34	14
12	45	9
13	56	5
14	58	7
15	47	4
16	80	3
17	23	4
18	23	4
19	58	6
20	23	9

13.9._

0	54	15
1	36	11
2	23	15
3	38	7
4	23	7
5	23	4
6	23	7
7	23	2
8	23	4
9	23	11
10	23	8
11	23	9
12	38	5
13	31	7
14	23	2
15	47	4
16	23	2
17	23	3
18	23	4
19	38	5
20	23	8

13.10.L

0	23	13
1	23	6
2	52	5
3	23	5
4	23	4
5	23	1
6	54	7
7	23	4
8	34	8
9	23	5

14.0.L

0	23	13
1	20	19
2	38	13
3	20	6
4	20	9
5	40	25
6	20	21
7	38	13
8	23	42
9	23	1
10	23	19
11	47	35
12	23	18
13	23	23
14	47	18
15	49	11
16	23	10
17	56	13
18	69	52
19	63	24
20	23	25

14.1.L

0	20	10
1	23	27
2	23	22
3	45	27
4	31	19
5	43	16
6	34	13
7	47	16
8	45	20
9	45	9
10	23	29
11	65	34
12	23	9
13	52	17
14	23	17
15	52	19
16	43	23
17	23	24
18	40	14
19	20	8
20	56	27

14.2.L

0	36	12
1	49	24

14.2.L

2	34	4
3	23	20
4	23	33
5	23	11
6	23	24
7	65	19
8	20	24
9	43	24
10	23	8
11	20	8
12	23	0
13	49	13
14	20	15
15	23	19
16	23	9
17	56	23
18	20	8
19	23	2
20	23	18

14.3.L

0	45	8
1	23	19
2	20	5
3	20	5
4	23	28
5	36	20
6	34	31
7	23	11
8	20	15
9	20	10
10	23	15
11	20	6
12	31	18
13	63	19
14	23	14
15	34	10
16	23	11
17	23	6
18	23	23
19	23	11
20	23	9

14.4.L

0	43	2
1	20	9
2	23	18
3	23	31
4	52	11
5	45	11
6	20	8
7	23	7
8	23	8
9	23	14
10	20	18
11	23	15
12	69	11
13	52	16
14	20	3
15	23	16
16	36	19
17	23	9
18	23	6
19	23	3
20	49	2

14.5.L

0	20	13
1	20	12
2	23	4
3	23	7
4	20	9
5	20	20
6	31	20
7	56	10
8	23	19
9	23	3
10	23	10
11	23	2
12	23	8
13	43	12
14	36	4
15	23	7
16	36	7
17	23	5
18	38	14
19	49	9
20	60	10

14.6.L

0	23	6
1	34	22
2	56	11
3	40	16
4	23	9
5	23	8
6	23	11
7	20	16
8	58	5
9	45	16
10	23	8
11	23	9
12	56	12
13	60	13
14	38	10
15	23	9
16	23	6
17	29	3
18	23	3
19	47	3
20	23	5

14.7.L

0	23	5
1	67	9
2	23	5
3	23	12
4	20	13
5	23	4
6	23	11
7	23	8
8	47	6
9	52	15
10	23	14
11	40	9
12	23	8
13	47	4
14	31	6
15	23	3
16	23	15
17	43	4
18	23	5
19	23	6
20	23	14

14.8.L

0	23	12
1	23	5
2	23	10
3	23	5
4	63	5
5	23	7
6	63	8
7	45	4
8	38	9
9	23	3
10	23	5
11	49	9
12	23	2
13	23	8
14	23	2
15	23	4
16	23	4
17	54	7
18	63	13
19	23	5
20	60	5

14.9.L

0	54	6
1	23	2
2	74	13
3	20	8
4	56	4
5	23	4
6	38	5
7	54	4
8	23	6
9	23	4
10	67	3
11	23	9

15.0.L

0	20	0
1	56	11
2	23	2
3	20	10
4	47	7
5	34	5
6	23	7
7	60	19
8	20	13
9	23	15
10	20	3
11	40	6
12	23	3
13	52	2
14	36	2
15	23	15
16	31	0
17	49	16
18	52	5
19	23	14
20	23	11

15.1.L

0	23	20
1	58	3
2	43	9
3	54	7
4	54	10
5	47	8
6	23	15
7	52	6
8	31	12
9	23	4
10	40	14
11	36	5

15.1.L

12	20	11
13	23	4
14	40	12
15	36	9
16	23	10
17	20	5
18	34	7
19	23	8
20	23	5

15.2.L

0	36	5
1	23	7
2	36	6
3	20	16
4	34	10
5	47	14
6	67	3
7	49	8
8	43	3
9	20	7
10	23	8
11	20	13
12	23	6
13	23	13
14	23	4
15	34	10
16	23	1
17	23	3
18	23	4
19	23	13
20	23	4

15.3.L

0	20	5
1	60	8
2	23	14
3	23	2
4	36	17
5	23	7
6	23	12
7	31	7
8	63	7
9	20	6
10	23	9
11	20	5
12	52	11
13	38	3
14	23	7
15	23	1
16	20	12
17	23	2
18	23	13
19	43	3
20	23	6

15.4.L

0	34	16
1	23	13
2	23	6
3	23	9
4	23	8
5	40	7
6	23	5
7	31	10
8	23	1
9	23	12
10	23	5
11	23	9
12	23	8
13	23	10
14	23	8
15	23	7
16	23	8
17	58	0
18	58	3
19	31	3
20	23	2

15.5.L

0	23	2
1	23	11
2	23	11
3	23	12
4	45	9
5	31	13
6	20	7
7	23	13
8	23	6
9	45	5
10	58	4
11	23	4
12	38	6
13	23	3
14	36	9
15	34	7
16	20	8
17	40	6
18	45	8
19	23	2
20	31	7

15.6.L

0	43	3
1	23	5
2	23	7
3	60	8
4	45	9
5	40	12
6	23	4
7	23	6
8	63	11
9	23	7
10	58	6
11	23	13
12	23	7
13	23	3
14	49	10
15	23	2
16	36	7
17	23	5

APPENDIX B

X-RAY DATA OF MORPHINE METHYLIODIDE

0,0,L

2	218	219
4	1333	1216
6	629	572
8	875	851
10	901	914
12	401	410
14	646	658
16	263	262

0,1,L

1	481	497
3	68	35
4	1220	1093
5	875	786
6	1384	1254
7	507	462
8	1379	1301
9	845	800
10	252	250
11	38	67
12	979	970
13	396	412
14	22	86
15	160	167
16	491	497
17	24	11

0,2,L

0	68	107
3	1051	916
4	1243	1079
5	189	131
6	787	758
7	471	432
8	418	363
9	467	444
10	1101	1040
11	321	318
12	19	16
13	297	305
14	709	706
15	233	249
16	401	414
17	144	163

0,3,L

3	212	197
4	360	320
5	473	448
6	602	516
7	260	233
8	464	423
9	821	776
10	73	82
11	437	420
12	476	477
13	248	218
14	309	312
15	405	418
16	428	434
17	22	38

0,4,L

0	869	870
1	343	328
2	442	373
3	1207	1084
4	830	695
5	294	269
6	379	352
7	1071	998
8	646	602
9	277	277
10	459	439
11	585	548
12	75	80
13	561	540
14	211	208
15	265	246
16	102	123
17	678	678

0,5,L

1	1508	1391
2	518	456
3	133	148
4	216	188
5	1462	1289
6	338	291
7	167	158
8	197	184
9	841	793
10	70	68
11	614	567
12	53	24
13	476	458
14	235	226
15	277	274
16	85	75
17	41	59

0,6,L

0	301	322
1	665	631
2	240	220
3	1278	1147
4	73	49
5	65	51
6	21	30
7	1000	943
8	316	284
9	348	312
10	229	210
11	559	546
12	110	97
13	355	365
14	207	189
15	90	84
16	41	8
17	253	260

0,7,L

1	576	581
2	782	712
3	321	313
4	219	212
5	597	565
6	204	182
7	32	44
8	342	325
9	586	560
10	21	12
11	382	346
12	70	58
13	48	26
14	22	33
15	473	474
16	143	150
17	48	70

0,8,L

0	316	327
1	141	155
2	609	597
3	479	438
4	474	410
5	60	25
6	335	308
7	592	560
8	265	247
9	195	177
10	398	380
11	223	218
12	55	40
13	163	146
14	138	130
15	34	36
16	46	60
17	150	152

0,9,L

1	139	138
2	320	310
3	146	132
4	340	306
5	296	272
6	331	297
7	58	20
8	491	464
9	248	243
10	207	212
11	150	150
12	372	371
13	22	37
14	185	172
15	95	115
16	399	390
17	65	18

0,10,L

0	624	675
1	126	125
2	21	17
3	21	38
4	270	261
5	38	19
6	473	438
7	22	9
8	311	301
9	168	172
10	401	384
11	55	87
12	22	30
13	107	118
14	269	272
15	24	14
16	70	78
17	109	105

0,11,L

1	124	128
2	439	427
3	21	31
4	263	248
5	22	6
6	381	359

0,11,L

7	151	143
8	335	300
9	68	81
10	48	8
11	73	2
12	252	248
13	46	48
14	24	33
15	284	273
16	68	26
17	102	120

0,12,L

0	272	305
1	122	119
2	92	80
3	155	148
4	282	269
5	73	23
6	190	154
7	133	123
8	55	57
9	148	143
10	352	348
11	170	166
12	87	18
13	88	70
14	92	85
15	104	98
16	61	32
17	68	14

1,0,L

1	585	637
2	207	200
3	1319	1196
4	58	29
5	99	67
6	66	54
7	1776	1644
8	195	208
9	309	296
10	347	351
11	847	819
12	17	11
13	677	662
14	199	204
15	104	97
16	95	107
17	466	485

1,1,L

0	49	68
1	838	855
2	221	220
3	1149	1063
4	364	315
6	304	277
7	219	213
8	180	162
9	940	866
10	121	112
11	641	627
12	333	326
13	357	358
14	102	118
15	580	602
16	105	118
17	95	111

1,2,L

0	428	412
1	986	1025
2	306	274
4	1288	1147
5	530	465
6	874	791
7	1203	1109
8	605	553
9	527	495
10	709	681
11	712	699
12	73	28
13	481	470
14	440	431
15	240	256
16	267	271
17	201	201

1,3,L

0	495	555
1	510	516
3	357	310
4	508	479
5	1090	972
6	1054	946
7	503	450
8	957	881
9	886	830
10	233	219
11	231	241
12	666	657
13	350	337
14	277	266
15	311	314
16	314	321
17	53	53

1,4,L

0	1707	1775
1	677	694
2	274	211
3	377	336
4	1501	1333
5	253	196
6	1171	1081
7	194	187
8	469	432
9	308	294
10	894	852
11	153	123
12	95	78
13	199	199
14	422	422
15	105	96
16	214	213
17	151	161

1,5,L

0	253	240
1	275	254
2	1028	978
3	534	505
4	578	533
5	85	64
6	826	760
7	17	24
8	1062	998
9	92	83
10	316	299
11	19	30
12	756	754
13	160	152
14	342	332
15	139	150
16	367	390
17	109	96

1,6,L

0	988	1054
1	447	463
2	399	383
3	355	355
4	994	945
5	180	139
6	721	667
7	309	296
8	258	259
9	83	77
10	736	716
11	139	136
12	173	186
13	190	188
14	632	638
15	136	142
16	269	261
17	126	107

1,7,L

0	82	9
1	185	211
2	1015	989
3	219	215
4	508	489
5	529	502
6	568	538
7	117	126
8	624	590
9	428	423
10	122	116
11	206	197
12	546	534
13	153	149
14	83	77
15	303	303
16	165	179
17	36	25

1,8,L

0	685	747
1	445	483
2	296	286
3	549	534
4	615	569
5	223	222
6	309	277
7	464	447
8	177	160
9	280	266
10	379	362
11	394	385
12	105	128
13	382	380
14	277	286
15	155	156
16	218	215
17	228	230

1,9,L

0	156	205
1	549	599
2	357	350
3	428	421
4	241	232
5	661	660
6	126	106
7	165	166
8	243	225
9	325	316
10	109	106
11	320	297
12	197	192
13	272	264
14	48	61
15	126	140
16	121	128
17	104	87

1,10,L

0	112	116
1	311	348
2	99	112
3	578	593
4	46	24
5	119	106
6	165	156
7	461	461
8	85	83
9	148	135
10	102	102
11	240	236
12	24	26
13	284	282
14	97	90
15	24	45
16	72	77
17	199	202

1,11,L

0	58	41
1	343	382
2	100	89
3	155	174
4	22	39
5	398	393
6	56	42
7	95	92
8	139	140
9	284	284
10	41	26
11	180	169
12	76	77
13	131	141
14	155	136
15	321	322
16	148	141
17	26	51

1,12,L

0	80	59
1	184	207
2	53	9
3	311	320
4	129	143
5	48	39
6	102	96
7	262	270
8	129	122
9	100	73
10	97	83
11	136	148
12	24	22
13	189	187
14	82	93
15	26	69
16	73	53
17	202	213

2,0,L

1	131	176
2	1095	1203
3	597	567
5	90	47
6	1168	1167
7	92	94
8	87	81
9	437	400
10	1234	1212
11	257	274
12	105	90
13	195	204
14	751	772
15	192	221
16	313	329
17	105	98

2,1,L

0	133	162
1	836	915
3	267	263
4	981	955
5	433	413
6	884	842
7	269	251
8	1246	1210
9	280	257
10	369	368
11	58	80
12	762	749
13	150	125
14	331	336
15	202	209
16	530	555
17	21	5

2,2,L

1	918	998
2	61	80
3	792	799
4	1234	1177
5	399	384
6	687	644
7	539	519
8	629	629
9	325	306
10	739	722
11	456	429
12	116	102
13	320	322
14	707	720
15	141	147
16	367	372
17	296	301

2,3,L

0	420	457
1	648	716
2	1095	1149
3	161	163
4	525	500
5	1205	1160
6	850	806
7	350	325
8	529	519
9	814	780
10	53	61
11	396	396
12	714	693
13	495	510
14	71	47
15	427	432
16	235	250
17	21	15

2,4,L

0	122	160
1	563	637
2	445	475
3	1256	1249
4	651	619
5	126	116
6	607	582
7	884	849
8	224	217
9	326	326
10	394	390
11	694	685
12	158	155
13	578	586
14	167	180
15	289	297
16	199	200
17	391	402

2,5,L

0	180	154
1	1125	1209
2	410	418
3	561	570
4	139	122
5	947	938
6	194	166
7	165	151
8	139	134
9	668	631
10	156	141
11	513	502
12	105	107
13	343	355
14	199	194
15	457	462
16	124	129
17	22	13

2,6,L

0	51	17
1	510	555
2	372	372
3	1052	1061
4	255	242
5	87	81
6	224	209
7	1034	976
8	68	65
9	342	342
10	109	104

2,6,L

11	364	343
12	206	203
13	379	368
14	119	108
15	43	72
16	144	139
17	318	319

2,7,L

0	214	234
1	517	568
2	433	464
3	267	288
4	354	357
5	777	753
6	185	175
7	143	139
8	241	231
9	558	546
10	122	109
11	313	312
12	389	379
13	126	143
14	49	64
15	284	303
16	61	88
17	22	43

2,8,L

0	637	701
1	425	440
2	32	22
3	216	233
4	243	253
5	155	139
6	564	569
7	413	414
8	326	306
9	224	205
10	301	289
11	282	293
12	48	30
13	263	276
14	270	257
15	105	100
16	134	131
17	112	162

2,9,L

0	75	38
1	274	285
2	464	495
3	97	123
4	297	293
5	287	302
6	396	393
7	109	109
8	362	352
9	240	255
10	177	173
11	180	192
12	253	240
13	22	36
14	121	106
15	70	91
16	219	230
17	72	29

2,10,L

0	364	398
1	66	55
2	182	198
3	141	133
4	444	449
5	133	155
6	219	215
7	85	77
8	163	179
9	109	117
10	447	435
11	68	67
12	36	49
13	55	43
14	267	256
15	105	98
16	92	81
17	60	28

2,11,L

0	148	160
1	61	61
2	360	380
3	73	60
4	190	197
5	55	88
6	228	229
7	53	65
8	384	392
9	122	112
10	75	64
11	46	59
12	241	235
13	97	89
14	95	108
15	102	82
16	133	151
17	26	36

2,12,L

0	245	261
1	161	169
2	112	106
3	168	176
4	282	294
5	55	46
6	236	251
7	136	143
8	107	101
9	87	118
10	240	239
11	82	82
12	56	67
13	126	102
14	78	111
15	26	43
16	99	59
17	117	83

3,0,L

1	1008	1111
2	218	214
3	1390	1467
4	31	55
5	547	548
6	87	50
7	1280	1286
8	15	12
9	444	464
10	54	71
11	692	712
12	178	184
13	501	516
14	29	35
15	170	172
16	150	168
17	371	399

3,1,L

0	252	289
1	896	1003
2	717	794
3	321	325
4	530	505
5	1134	1142
6	722.	734
7	231	224
8	337	325
9	1056	1027
10	38	53
11	724	742
12	391	390
13	496	507
14	104	123
15	347	361
16	170	189
17	34	41

3,2,L

0	1045	1139
1	700	760
2	427	453
3	654	715
4	699	713
5	127	114
6	399	398
7	1112	1089
8	471	478
9	469	469
10	588	575
11	226	206
12	214	191
13	474	482
14	190	191
15	178	175
16	114	97
17	374	395

3,3,L

0	83	74
1	1032	1097
2	677	735
3	304	315
4	688	680
5	746	719
6	656	655
7	107	119
8	891	860
9	484	480
10	68	91
11	204	217
12	620	623
13	184	190
14	194	194
15	362	370
16	226	228
17	63	84

3,4,L

0	1011	1068
1	83	67
2	158	178
3	495	505
4	830	854
5	61	59
6	847	828
7	267	266
8	490	467
9	194	182
10	949	916
11	520	518
12	311	321
13	153	157
14	583	586
15	141	148
16	255	264
17	22	45

3,5,L

0	15	13
1	158	158
2	1198	1246
3	136	153
4	505	527
5	240	215
6	864	849
7	238	221
8	952	916
9	39	38
10	255	247
11	93	81
12	442	441
13	178	177
14	156	148
15	87	94
16	369	385
17	55	60

3,6,L

0	1139	1222
1	75	74
2	335	367
3	116	110
4	790	789
5	248	231
6	345	337
7	376	378
8	512	520
9	201	195
10	775	769
11	318	325
12	85	81
13	124	129
14	381	396
15	177	165
16	178	196
17	65	61

3,7,L

0	66	87
1	325	341
2	576	620
3	330	346
4	372	383
5	326	342
6	388	391
7	185	187
8	503	494
9	430	438
10	21	48
11	185	182
12	549	545
13	107	102
14	158	157
15	214	208
16	274	294
17	112	127

3,8,L

0	343	373
1	301	327
2	337	350
3	503	524
4	445	453
5	187	195
6	563	576
7	462	462
8	136	120
9	156	153
10	320	314
11	240	238
12	44	52
13	194	187
14	202	220
15	51	66
16	141	125
17	173	162

3,9,L

0	267	255
1	437	480
2	447	468
3	85	101
4	189	206
5	493	510
6	199	207
7	60	20
8	189	173
9	422	428
10	88	103
11	338	341
12	192	195
13	136	134
14	85	67
15	267	253
16	80	95
17	38	26

3,10,L

0	221	215
1	246	281
2	87	43
3	539	571
4	21	14
5	44	35
6	71	52
7	435	443
8	75	42
9	280	288
10	75	77
11	221	223
12	46	37
13	265	256
14	112	111
15	51	69
16	63	69
17	236	242

3,11,L

0	138	154
1	371	405
2	78	85
3	182	184
4	63	45
5	330	333
6	51	69
7	55	67
8	66	64
9	252	264
10	78	61
11	173	181
12	24	51
13	182	214
14	61	38
15	129	141
16	90	46
17	39	11

3,12,L

0	58	55
1	250	276
2	75	80
3	146	155
4	76	74
5	41	64
6	58	73
7	235	245
8	127	131
9	55	38
10	133	129
11	180	215
12	53	57
13	158	149
14	46	69
15	26	75
16	26	5
17	100	126

4,0,L

0	918	1017
1	65	87
2	54	23
3	270	280
4	602	684
5	382	366
6	1518	1551
7	15	22
8	386	430
9	48	54
10	765	792
11	229	231
12	88	26
13	194	197
14	755	792
15	216	232
16	357	376
17	21	14

4,1,L

0	71	43
1	362	385
2	1413	1572
3	272	264
4	1076	1115
5	571	583
6	702	728

4,1,L

7	297	305
8	648	658
9	100	111
10	204	204
11	138	145
12	687	713
13	172	186
14	294	300
15	194	208
16	362	398
17	21	4

4,2,L

0	1044	1111
1	309	356
2	432	463
3	682	737
4	1248	1289
5	151	138
6	671	708
7	505	529
8	413	422
9	187	200
10	709	730
11	493	499
12	214	226
13	474	498
14	437	458
15	126	129
16	211	214
17	236	245

4,3,L

0	151	136
1	733	789
2	539	595
3	731	746
4	221	240
5	882	921
6	365	382
7	150	180
8	678	673
9	498	512
10	277	274
11	216	239
12	668	687
13	447	454
14	21	32
15	467	478
16	229	254
17	76	82

4,4,L

0	541	555
1	626	679
2	165	167
3	1088	1137
4	384	382
5	112	112
6	335	319
7	746	749
8	138	107
9	212	218
10	204	217
11	564	574
12	235	248
13	318	314
14	182	201
15	76	81
16	126	124
17	270	272

4,5,L

0	219	166
1	617	677
2	241	259
3	284	315
4	243	235
5	874	883
6	124	102
7	180	176
8	297	294
9	479	484
10	63	68
11	466	471
12	44	53
13	379	385
14	61	54
15	416	437
16	65	63
17	104	92

4,6,L

0	250	253
1	568	600
2	80	83
3	736	788
4	158	175
5	65	65
6	178	180
7	614	620
8	151	164
9	410	407
10	158	153
11	335	337
12	46	41
13	461	477
14	49	57
15	95	82
16	53	78
17	297	314

4,7,L

0	187	181
1	532	563
2	338	372
3	308	321
4	282	297
5	682	703
6	144	135
7	265	272
8	257	265
9	484	487
10	124	142
11	214	230
12	253	239
13	199	205
14	90	90
15	233	231
16	83	80
17	44	21

4,8,L

0	452	491
1	311	337
2	129	148
3	262	278
4	488	537
5	218	220
6	231	239
7	320	326
8	51	59
9	131	141
10	331	311
11	228	244
12	44	38
13	212	224
14	299	306
15	76	56
16	148	136
17	131	144

4,9,L

0	107	102
1	99	107
2	552	599
3	83	98
4	143	154
5	192	201
6	263	265
7	65	57
8	294	288
9	185	195
10	136	140
11	95	94
12	275	266
13	22	38
14	38	39
15	122	117
16	136	141
17	24	13

4,10,L

0	469	496
1	60	36
2	97	88
3	102	107
4	287	297
5	55	43
6	314	334
7	109	108
8	209	208
9	75	82
10	272	274
11	105	107
12	24	42
13	100	109
14	258	249
15	24	52
16	90	97
17	39	11

4,11,L

0	60	56
1	41	45
2	258	275
3	22	52
4	263	271
5	92	103
6	294	311
7	22	39
8	263	273
9	117	101
10	22	10
11	105	118
12	224	231
13	87	85

4,11,L

14	133	128
15	24	16
16	114	120
17	73	18

4,12,L

0	212	217
1	133	146
2	168	177
3	163	166
4	340	344
5	109	103
6	199	202
7	105	105
8	80	90
9	72	66
10	178	173
11	122	77
12	80	82
13	129	116
14	73	86
15	70	57
16	124	109
17	66	67

5,0,L

1	933	1017
2	14	5
3	894	1012
4	267	251
5	704	703
6	87	56
7	858	909
8	82	89
9	377	406
10	126	124
11	345	354
12	311	325
13	415	433
14	109	90
15	204	209
16	21	12
17	379	417

5,1,L

0	43	21
1	838	943
2	104	108
3	447	469
4	199	212
5	734	794
6	328	319
7	172	181
8	330	350
9	864	923
10	189	191
11	467	489
12	367	381
13	284	287
14	85	108
15	371	378
16	73	71
17	22	22

5,2,L

0	741	752
1	388	416
2	80	98
3	772	842
4	603	623
5	156	178
6	252	259
7	663	705
8	156	156
9	461	467
10	474	489
11	444	476
12	258	260
13	444	453
14	231	253
15	44	58
16	87	108
17	270	289

5,3,L

0	117	87
1	590	626
2	801	837
3	199	180
4	304	317
5	692	718
6	518	534
7	99	103
8	801	807
9	269	269
10	53	75
11	345	354
12	369	386
13	105	111
14	129	140
15	253	268
16	184	210
17	22	36

5,4,L

0	1015	1055
1	435	437
2	320	350
3	127	135
4	714	734
5	258	253
6	522	519
7	432	454
8	435	449
9	131	131
10	726	743
11	161	179
12	184	187
13	184	182
14	352	369
15	22	46
16	177	185
17	163	169

5,5,L

0	17	9
1	165	158
2	789	846
3	61	62
4	513	521
5	75	70
6	675	703
7	243	247
8	653	659
9	185	183
10	146	160
11	114	107
12	452	471
13	43	52
14	127	135
15	102	116
16	321	338
17	116	98

5,6,L

0	624	651
1	284	294
2	250	259
3	19	47
4	537	560
5	95	97
6	573	583
7	316	310
8	449	445
9	70	94
10	554	560
11	136	145
12	21	44
13	121	111
14	362	381
15	109	95
16	112	116
17	75	56

5,7,L

0	82	64
1	257	260
2	576	603
3	127	129
4	291	310
5	381	384
6	386	400
7	189	199
8	362	373
9	275	290
10	122	131
11	122	145
12	355	370
13	92	92
14	131	138
15	102	104
16	209	223
17	24	27

5,8,L

0	478	480
1	122	146
2	270	296
3	371	382
4	320	330
5	158	172
6	340	348
7	498	500
8	158	170
9	138	136
10	258	270
11	228	235
12	51	42
13	168	173
14	126	122
15	58	88
16	129	146
17	170	162

5,9,L

0	82	74

5,9,L

1	347	365
2	275	295
3	143	156
4	207	222
5	413	418
6	75	59
7	131	150
8	201	195
9	291	312
10	22	34
11	343	341
12	201	200
13	148	147
14	49	16
15	201	211
16	49	69
17	60	69

5,10,L

0	117	118
1	207	214
2	53	51
3	405	432
4	82	71
5	22	52
6	68	82
7	416	421
8	22	50
9	139	143
10	105	106
11	199	216
12	88	98
13	148	160
14	73	106
15	48	61
16	55	27
17	124	138

5,11,L

0	71	48
1	325	341
2	68	48
3	127	140
4	22	12
5	223	235
6	104	107
7	82	65
8	49	34
9	279	285
10	110	112
11	104	98
12	73	46
13	114	124
14	49	50
15	141	139
16	66	51
17	26	19

5,12,L

0	82	99
1	143	148
2	76	65
3	240	237
4	38	54
5	126	133
6	92	96
7	114	121
8	100	106
9	143	144
10	90	79
11	187	193
12	24	18
13	121	116
14	72	65
15	87	88
16	26	34
17	92	110

6,0,L

0	1197	1252
1	185	189
2	573	610
3	110	90
4	845	923
5	224	218
6	622	690
7	46	28
8	376	408
9	19	31
10	643	706
11	48	40
12	100	37
13	21	13
14	309	346
15	21	13
16	211	227
17	22	9

6,1,L

0	34	31
1	311	342
2	881	939
3	209	220
4	592	628
5	286	313
6	544	567
7	121	129
8	627	663
9	66	75
10	182	173
11	204	238
12	510	560
13	178	185
14	143	148
15	158	172
16	325	367
17	70	76

6,2,L

0	569	577
1	318	346
2	173	186
3	512	543
4	529	560
5	184	186
6	697	715
7	529	549
8	331	337
9	206	225
10	508	531
11	289	290
12	155	161
13	167	172
14	452	492
15	109	118
16	148	156
17	143	141

6,3,L

0	102	102
1	620	645
2	541	560
3	277	281
4	320	324
5	619	636
6	342	334
7	151	130
8	433	452
9	371	385
10	182	178
11	211	214
12	355	374
13	138	147
14	143	135
15	357	378
16	110	130
17	46	42

6,4,L

0	369	358
1	432	450
2	192	195
3	688	729
4	333	332
5	104	117
6	182	192
7	578	594
8	92	75
9	170	175
10	337	353
11	399	398
12	156	166
13	382	394
14	63	79
15	160	176
16	68	75
17	355	375

6,5,L

0	56	56
1	636	677
2	134	126
3	325	338
4	51	19
5	658	663
6	136	118
7	365	386
8	260	263
9	544	552
10	88	99
11	308	327
12	63	83
13	318	319
14	139	136
15	255	270
16	83	68
17	38	41

6,6,L

0	155	160
1	493	525
2	233	233
3	685	693
4	122	131
5	134	126
6	177	192
7	430	446

6,6,L

8	163	166
9	284	310
10	93	106
11	323	339
12	82	95
13	299	306
14	76	67
15	78	81
16	58	62
17	190	196

6,7,L

0	55	65
1	398	403
2	479	494
3	223	223
4	53	69
5	440	446
6	104	121
7	129	116
8	206	195
9	357	361
10	117	120
11	204	218
12	209	202
13	127	128
14	93	76
15	199	223
16	112	107
17	24	27

6,8,L

0	520	546
1	245	249
2	51	27
3	241	234
4	311	302
5	95	98
6	197	195
7	277	283
8	151	174
9	117	115
10	206	214
11	121	137
12	73	71
13	206	216
14	182	194
15	95	70
16	109	96
17	117	138

6,9,L

0	38	32
1	117	105
2	280	295
3	161	163
4	223	233
5	240	236
6	250	254
7	68	58
8	301	300
9	114	109
10	182	197
11	104	117
12	245	238
13	76	54
14	85	55
15	110	104
16	158	156
17	44	8

6,10,L

0	376	386
1	32	9
2	61	85
3	46	56
4	406	417
5	22	47
6	134	152
7	99	94
8	107	100
9	92	82
10	252	240
11	24	48
12	24	45
13	93	72
14	211	229
15	72	54
16	99	110
17	26	25

6,11,L

0	22	17
1	51	54
2	330	350
3	46	43
4	155	165
5	68	71
6	216	227
7	24	42
8	207	211
9	90	89
10	34	11
11	24	34
12	163	160
13	112	101
14	109	92
15	44	28
16	82	92
17	26	21

6,12,L

0	212	209
1	87	83
2	68	45
3	95	94
4	163	164
5	75	51
6	218	222
7	102	121
8	124	111
9	93	98
10	141	156
11	110	118
12	39	60
13	58	64
14	90	77
15	26	48
16	26	56
17	65	40

7,0,L

1	289	307
2	41	73
3	524	591
4	38	15
5	49	68
6	126	114
7	653	700
8	48	10
9	260	273
10	107	140
11	433	454
12	90	92
13	445	456
14	39	16
15	63	54
16	34	12
17	328	361

7,1,L

0	141	174
1	583	614
2	194	183
3	432	474
4	78	61
5	739	793
6	187	192
7	78	91
8	212	194
9	423	446
10	71	59
11	367	398
12	99	94
13	243	248
14	82	81
15	292	312
16	53	58
17	43	23

7,2,L

0	306	320
1	716	756
2	126	115
3	610	647
4	425	449
5	158	161
6	245	275
7	537	567
8	204	209
9	202	228
10	299	320
11	296	309
12	56	49
13	289	315
14	269	285
15	85	78
16	144	137
17	153	160

7,3,L

0	114	132
1	372	383
2	661	683
3	207	209
4	352	349
5	411	435
6	433	435
7	207	210
8	512	529
9	338	362
10	109	120
11	161	168
12	440	446
13	116	120
14	66	56
15	246	257

7,3,L

16	124	103
17	22	12

7,4,L

0	767	777
1	122	127
2	122	108
3	371	384
4	644	655
5	133	139
6	508	508
7	82	72
8	275	272
9	126	113
10	515	519
11	53	37
12	43	60
13	126	132
14	246	245
15	70	60
16	85	94
17	148	155

7,5,L

0	44	56
1	214	217
2	532	531
3	63	42
4	275	281
5	21	27
6	440	437
7	36	54
8	425	430
9	53	61
10	92	101
11	63	35
12	391	408
13	131	125
14	219	211
15	122	127
16	241	248
17	38	39

7,6,L

0	403	382
1	38	38
2	185	200
3	190	180
4	478	482
5	170	171
6	445	440
7	121	106
8	270	283
9	87	103
10	379	373
11	65	53
12	85	95
13	60	36
14	313	316
15	44	55
16	211	194
17	55	53

7,7,L

0	80	53
1	76	54
2	498	512
3	161	161
4	286	285
5	265	270
6	347	342
7	75	79
8	343	340
9	311	301
10	102	116
11	105	81
12	265	264
13	87	92
14	78	83
15	160	174
16	150	163
17	60	94

7,8,L

0	415	420
1	185	172
2	112	99
3	287	286
4	240	245
5	41	52
6	192	208
7	364	359
8	78	91
9	124	117
10	253	249
11	236	242
12	75	24
13	241	239
14	156	156
15	105	94
16	104	91
17	77	95

7,9,L

0	22	37
1	335	328
2	153	153
3	226	223
4	184	188
5	374	371
6	39	5
7	117	119
8	202	188
9	229	232
10	24	31
11	105	105
12	102	99
13	90	85
14	34	2
15	109	113
16	51	39
17	65	56

7,10,L

0	83	50
1	156	153
2	83	100
3	301	302
4	60	31
5	88	79
6	68	37
7	277	280
8	43	36
9	95	103
10	24	12
11	173	177
12	66	76
13	102	97
14	24	34
15	88	92
16	26	38
17	116	92

7,11,L

0	66	21
1	173	181
2	39	50
3	24	29
4	48	10
5	236	233
6	51	72
7	83	79
8	58	60
9	151	159
10	24	28
11	168	160
12	56	36
13	146	158
14	90	54
15	127	131
16	26	47
17	26	42

7,12,L

0	24	42
1	180	162
2	24	36
3	136	141
4	146	155
5	60	53
6	24	42
7	190	183
8	70	66
9	24	42
10	24	22
11	95	110
12	38	14
13	93	98
14	70	68
15	41	57
16	26	50
17	119	113

8,0,L

0	1039	1059
1	168	180
2	313	332
3	76	73
4	603	627
5	29	36
6	435	443
7	136	142
8	250	250
9	277	318
10	469	495
11	21	50
12	31	16
13	48	1
14	301	338
15	68	57
16	56	59
17	49	29

8,1,L

0	287	296
1	398	415

8,1,L

2	588	614
3	116	103
4	376	397
5	224	234
6	384	389
7	49	34
8	517	548
9	245	268
10	153	143
11	21	18
12	362	378
13	76	100
14	75	77
15	99	96
16	238	249
17	46	69

8,2,L

0	471	464
1	297	293
2	260	276
3	473	483
4	321	324
5	163	173
6	274	301
7	241	249
8	250	248
9	192	179
10	393	402
11	177	179
12	82	38
13	126	124
14	226	243
15	97	97
16	177	189
17	121	142

8,3,L

0	141	147
1	415	417
2	418	413
3	143	158
4	221	221
5	343	342
6	253	250
7	178	190
8	269	262
9	345	331
10	21	31
11	228	235
12	201	216
13	178	168
14	61	65
15	241	248
16	151	165
17	82	99

8,4,L

0	282	296
1	326	312
2	56	48
3	462	475
4	156	157
5	63	46
6	270	270
7	493	488
8	156	150
9	168	154
10	202	207
11	323	313
12	21	10
13	262	266
14	104	112
15	148	159
16	22	22
17	296	290

8,5,L

0	92	62
1	643	620
2	136	153
3	201	190
4	126	115
5	530	518
6	68	47
7	99	95
8	48	67
9	394	393
10	21	35
11	214	211
12	58	68
13	160	150
14	34	45
15	192	192
16	75	84
17	34	26

8,6,L

0	216	234
1	428	407
2	41	52
3	457	454
4	75	57
5	110	95
6	68	62
7	440	425
8	119	125
9	153	156
10	110	101
11	170	172
12	22	13
13	189	187
14	146	136
15	78	93
16	72	49
17	156	165

8,7,L

0	41	16
1	282	290
2	287	301
3	104	94
4	165	159
5	320	307
6	170	167
7	22	32
8	178	174
9	214	226
10	22	46
11	253	251
12	110	97
13	116	131
14	49	43
15	144	141
16	73	68
17	24	13

8,8,L

0	365	362
1	82	80
2	124	118
3	250	233
4	224	210
5	38	26
6	194	190
7	226	213
8	141	133
9	114	119
10	161	157
11	146	155
12	24	10
13	150	123
14	110	106
15	24	23
16	100	87
17	90	94

8,9,L

0	83	83
1	121	93
2	287	274
3	105	102
4	104	100
5	153	132
6	216	214
7	95	65
8	156	156
9	134	130
10	55	73
11	87	67
12	255	240
13	68	17
14	63	41
15	99	103
16	180	171
17	26	19

8,10,L

0	325	318
1	73	48
2	58	69
3	48	51
4	199	194
5	56	59
6	173	158
7	41	35
8	139	146
9	110	111
10	223	221
11	63	53
12	80	69
13	55	70
14	177	172
15	61	45
16	104	95
17	39	41

8,11,L

0	24	6
1	24	33
2	253	257
3	24	12
4	121	114
5	73	20
6	161	157
7	44	33
8	187	202

8,11,L

9	88	98
10	75	55
11	46	46
12	105	112
13	43	61
14	78	53
15	73	67
16	41	62
17	58	44

8,12,L

0	185	184
1	73	66
2	66	51
3	117	98
4	189	196
5	24	26
6	85	80
7	60	61
8	70	62
9	48	41
10	163	149
11	90	85
12	65	42
13	83	61
14	90	75
15	100	78
16	26	32
17	70	47

9,0,L

1	396	389
2	133	106
3	389	389
4	19	8
5	19	19
6	75	77
7	503	517
8	51	66
9	129	145
10	44	48
11	304	309
12	38	39
13	342	339
14	76	79
15	48	67
16	66	26
17	175	185

9,1,L

0	197	208
1	467	460
2	151	139
3	309	307
4	116	85
5	551	539
6	153	158
7	105	119
8	90	91
9	379	374
10	82	59
11	195	214
12	104	108
13	136	134
14	38	49
15	272	284
16	92	93
17	24	40

9,2,L

0	236	228
1	219	200
2	53	56
3	575	567
4	219	223
5	114	115
6	286	285
7	416	405
8	229	237
9	173	176
10	253	248
11	229	240
12	75	72
13	172	189
14	139	133
15	32	28
16	58	79
17	129	148

9,3,L

0	216	201
1	289	284
2	483	489
3	165	164
4	209	198
5	357	352
6	314	309
7	87	60
8	280	272
9	180	178
10	70	53
11	185	198
12	267	261
13	155	147
14	122	125
15	107	110
16	127	137
17	63	30

9,4,L

0	394	381
1	246	250
2	138	124
3	73	49
4	513	505
5	73	58
6	364	356
7	143	136
8	163	158
9	76	73
10	291	300
11	112	102
12	22	23
13	133	132
14	199	202
15	104	91
16	99	103
17	51	69

9,5,L

0	21	46
1	80	87
2	399	392
3	71	43
4	224	204
5	21	16
6	292	277
7	73	72
8	372	362
9	75	62
10	105	93
11	22	24
12	330	313
13	68	67
14	53	61
15	43	34
16	102	114
17	24	33

9,6,L

0	449	433
1	92	115
2	83	74
3	39	60
4	359	348
5	121	113
6	187	182
7	151	141
8	99	84
9	60	41
10	304	297
11	92	78
12	22	40
13	70	57
14	282	270
15	39	29
16	99	94
17	24	17

9,7,L

0	110	110
1	148	144
2	326	317
3	129	119
4	182	169
5	195	168
6	160	144
7	75	62
8	280	266
9	131	116
10	109	92
11	114	116
12	216	202
13	139	140
14	63	63
15	95	72
16	119	112
17	77	56

9,8,L

0	248	232
1	185	176
2	112	100
3	212	198
4	195	192
5	126	101
6	218	219
7	163	156
8	83	87
9	95	82
10	112	109
11	167	152
12	56	34
13	144	133
14	66	94
15	24	20
16	72	95

9,8,L

17	90	92

9,9,L

0	24	6
1	192	183
2	150	146
3	144	133
4	105	107
5	270	260
6	110	105
7	56	77
8	66	83
9	218	193
10	82	60
11	97	68
12	26	61
13	95	71
14	78	59
15	82	86
16	41	46
17	90	74

9,10,L

0	51	45
1	180	179
2	63	51
3	209	208
4	63	28
5	75	49
6	24	35
7	211	193
8	24	5
9	72	97
10	68	57
11	92	95
12	41	32
13	139	125
14	43	35
15	109	111
16	68	32
17	97	106

9,11,L

0	70	54
1	143	134
2	75	84
3	95	93
4	77	83
5	206	180
6	87	49
7	99	97
8	95	76
9	141	131
10	41	32
11	26	49
12	26	8
13	70	68
14	26	7
15	136	114
16	53	32
17	55	17

9,12,L

0	102	72
1	73	33
2	44	71
3	172	154
4	80	54
5	48	29
6	72	73
7	90	87
8	55	29
9	66	40
10	83	76
11	99	95
12	26	16
13	27	63
14	75	76
15	60	41
16	87	76
17	63	64

10,0,L

0	508	491
1	71	66
2	173	164
3	21	39
4	355	335
5	99	92
6	323	317
7	38	7
8	127	124
9	70	43
10	282	292
11	109	98
12	41	24
13	104	86
14	212	219
15	88	97
16	153	144
17	24	32

10,1,L

0	48	44
1	212	194
2	500	460
3	60	50
4	241	236
5	190	170
6	279	263
7	43	40
8	289	271
9	55	41
10	41	47
11	124	114
12	291	278
13	92	87
14	22	30
15	53	23
16	119	115
17	83	73

10,2,L

0	525	496
1	253	241
2	80	60
3	255	239
4	320	300
5	76	55
6	185	171
7	178	165
8	151	141
9	104	107
10	260	246
11	124	117
12	22	18
13	143	152
14	228	212
15	107	84
16	82	80
17	119	112

10,3,L

0	88	80
1	301	283
2	219	203
3	194	174
4	117	115
5	328	303
6	138	120
7	102	98
8	236	232
9	297	289
10	105	95
11	119	101
12	139	125
13	216	204
14	100	87
15	122	111
16	148	142
17	46	51

10,4,L

0	71	50
1	335	296
2	150	148
3	367	341
4	151	147
5	112	89
6	136	116
7	309	274
8	100	68
9	95	94
10	48	53
11	236	213
12	22	54
13	173	164
14	34	35
15	102	81
16	72	76
17	151	147

10,5,L

0	60	41
1	335	311
2	112	92
3	121	95
4	22	17
5	369	328
6	88	96
7	66	51
8	22	36
9	240	222
10	80	70
11	168	147
12	82	61
13	80	79
14	95	91
15	258	234
16	44	65
17	44	58

10,6,L

0	155	146
1	122	82
2	22	8

10,6,L

3	399	361
4	90	72
5	55	53
6	80	46
7	371	342
8	58	35
9	141	129
10	51	46
11	172	167
12	24	47
13	138	132
14	70	45
15	46	73
16	51	48
17	138	128

10,7,L

0	22	39
1	297	274
2	167	160
3	138	111
4	167	146
5	297	264
6	134	114
7	60	47
8	109	111
9	201	185
10	55	55
11	119	104
12	78	53
13	24	50
14	24	68
15	136	124
16	117	105
17	48	23

10,8,L

0	158	139
1	131	111
2	163	150
3	153	140
4	207	182
5	97	82
6	182	165
7	165	144
8	107	112
9	87	74
10	219	191
11	129	112
12	24	30
13	85	94
14	146	134
15	26	53
16	58	32
17	66	69

10,9,L

0	73	22
1	48	49
2	245	224
3	24	22
4	110	106
5	46	58
6	151	135
7	78	44
8	134	133
9	88	80
10	66	75
11	85	95
12	156	135
13	51	64
14	26	28
15	26	26
16	104	101
17	26	46

10,10,L

0	151	153
1	63	54
2	65	61
3	24	14
4	146	139
5	90	81
6	146	123
7	51	63
8	124	98
9	53	29
10	170	166
11	26	17
12	26	43
13	26	23
14	85	89
15	26	22
16	27	45
17	49	16

10,11,L

0	61	47
1	36	16
2	165	158
3	24	18
4	87	82
5	24	31
6	124	109
7	51	33
8	153	131
9	26	31
10	51	19
11	73	18
12	122	131
13	60	39
14	82	21
15	46	25
16	26	60
17	27	10

10,12,L

0	226	209
1	48	55
2	26	32
3	55	63
4	102	92
5	38	16
6	114	107
7	80	73
8	68	59
9	26	17
10	90	98
11	38	30
12	77	45
13	56	27
14	43	64
15	26	6
16	51	33
17	27	37

11,0,L

1	236	193
2	21	5
3	418	393
4	73	33
5	119	110
6	21	22
7	430	399
8	80	92
9	109	97
10	22	4
11	238	231
12	83	88
13	104	103
14	102	92
15	73	56
16	88	83
17	144	147

11,1,L

0	70	61
1	301	274
2	134	139
3	124	100
4	56	36
5	354	330
6	95	85
7	55	44
8	127	117
9	318	294
10	102	96
11	155	166
12	117	80
13	82	87
14	61	38
15	187	179
16	127	116
17	24	39

11,2,L

0	172	156
1	182	159
2	122	85
3	252	217
4	209	186
5	76	61
6	160	137
7	308	281
8	144	136
9	150	137
10	146	139
11	168	155
12	73	17
13	180	182
14	56	81
15	75	73
16	44	48
17	107	102

11,3,L

0	22	24
1	216	194
2	243	216
3	73	66
4	150	139
5	255	222
6	223	196
7	93	71
8	218	196
9	163	155
10	73	55

11,3,L

11	124	120
12	95	93
13	85	88
14	124	117
15	78	52
16	131	117
17	85	37

11,4,L

0	311	268
1	88	48
2	134	113
3	199	169
4	265	233
5	117	77
6	214	187
7	78	73
8	134	112
9	90	91
10	277	248
11	143	141
12	85	59
13	83	65
14	165	145
15	49	51
16	61	76
17	73	48

11,5,L

0	63	51
1	102	85
2	359	326
3	41	25
4	129	118
5	71	27
6	246	212
7	24	53
8	236	206
9	80	57
10	43	28
11	60	16
12	280	253
13	85	84
14	24	39
15	51	23
16	85	66
17	24	11

11,6,L

0	364	336
1	100	90
2	36	16
3	138	113
4	235	207
5	138	108
6	160	130
7	24	42
8	151	118
9	109	97
10	201	186
11	78	65
12	24	34
13	24	8
14	122	130
15	26	25
16	68	65
17	60	32

11,7,L

0	56	38
1	141	112
2	187	167
3	170	163
4	117	97
5	44	52
6	107	93
7	66	47
8	184	157
9	88	86
10	78	52
11	117	85
12	136	131
13	55	61
14	65	48
15	26	16
16	68	68
17	63	25

11,8,L

0	219	201
1	199	186
2	24	36
3	90	70
4	131	108
5	39	28
6	107	95
7	156	126
8	68	19
9	48	33
10	88	88
11	78	66
12	82	48
13	102	79
14	78	88
15	68	58
16	80	44
17	63	50

11,9,L

0	26	26
1	124	122
2	134	117
3	76	33
4	68	57
5	172	153
6	63	35
7	87	81
8	77	56
9	153	134
10	48	22
11	102	85
12	73	39
13	77	44
14	53	59
15	85	76
16	46	61
17	26	40

11,10,L

0	73	53
1	148	134
2	95	68
3	180	153
4	38	33
5	80	58
6	56	5
7	107	102
8	26	7
9	85	73
10	55	22
11	61	63
12	26	33
13	143	103
14	26	21
15	26	17
16	26	15
17	66	72

11,11,L

0	99	88
1	167	145
2	66	16
3	58	68
4	70	15
5	124	120
6	26	10
7	26	25
8	95	70
9	73	58
10	26	24
11	27	43
12	26	16
13	41	49
14	38	31
15	41	54
16	26	13
17	26	24

11,12,L

0	26	27
1	26	29
2	61	55
3	87	84
4	61	42
5	82	44
6	41	23
7	82	75
8	43	28
9	78	30
10	83	61
11	70	47
12	55	21
13	27	40
14	55	31
15	27	40
16	27	15
17	60	49

12,0,L

0	284	247
1	22	42
2	121	96
3	22	21
4	304	270
5	88	79
6	153	125
7	22	19
8	22	17
9	55	27
10	204	189
11	92	95
12	24	41
13	77	87
14	177	155
15	148	134
16	87	91
17	24	19

12,1,L

0	22	14
1	83	61
2	318	289
3	110	87
4	158	127
5	73	58
6	146	121
7	93	87
8	192	170
9	39	31
10	92	53
11	80	72
12	211	179
13	24	40
14	55	54
15	24	32
16	82	77
17	24	24

12,2,L

0	299	264
1	93	87
2	55	13
3	209	186
4	265	220
5	63	49
6	194	161
7	109	89
8	138	115
9	66	74
10	131	112
11	155	135
12	75	52
13	150	122
14	150	134
15	46	19
16	82	64
17	75	61

12,3,L

0	22	15
1	236	207
2	197	170
3	156	117
4	80	69
5	252	216
6	167	132
7	34	33
8	83	69
9	155	132
10	70	37
11	114	76
12	92	90
13	148	131
14	95	72
15	121	88
16	102	91
17	56	32

12,4,L

0	114	100
1	216	186
2	38	43
3	246	201
4	36	38
5	24	42
6	77	80
7	236	202
8	24	18
9	82	60
10	48	43
11	156	140
12	90	75
13	138	112
14	61	31
15	83	50
16	63	40
17	92	88

12,5,L

0	24	31
1	190	163
2	24	8
3	105	64
4	24	34
5	280	227
6	24	34
7	112	97
8	24	10
9	201	176
10	70	63
11	95	55
12	26	12
13	92	64
14	41	27
15	151	145
16	26	18
17	26	20

12,6,L

0	83	76
1	170	123
2	44	34
3	257	208
4	51	26
5	46	33
6	80	70
7	207	174
8	24	11
9	109	84
10	51	43
11	121	90
12	51	26
13	151	127
14	72	42
15	26	27
16	26	18
17	109	75

12,7,L

0	60	53
1	167	127
2	93	88
3	68	61
4	146	107
5	233	196
6	68	44
7	24	22
8	129	92
9	105	87
10	26	48
11	102	92
12	88	77
13	87	74
14	95	40
15	65	65
16	80	49
17	26	12

12,8,L

0	134	123
1	24	17
2	24	37
3	131	109
4	143	105
5	70	28
6	143	131
7	161	128
8	80	74
9	44	35
10	122	85
11	121	80
12	26	34
13	92	61
14	78	84
15	61	43
16	26	34
17	68	62

12,9,L

0	66	34
1	53	45
2	158	129
3	65	41
4	104	95
5	61	47
6	150	125
7	66	20
8	92	65
9	26	68
10	75	37
11	65	31
12	131	111
13	26	18
14	63	5
15	26	28
16	68	44
17	46	2

12,10,L

0	95	74
1	63	33
2	39	51
3	70	6
4	167	134
5	26	13
6	121	100
7	85	35
8	107	65
9	27	51
10	97	86
11	56	15
12	26	23
13	26	34
14	102	81
15	27	30
16	53	44
17	27	4

12,11,L

0	26	36
1	72	22
2	121	108
3	26	48
4	78	62
5	68	32
6	70	42

APPENDIX C

X-RAY DATA OF COMPOUND I

-10,0,L

0	39*	25
2	250	246
4	13*	22
6	90	92
8	28*	36
10	17*	1
12	51*	21
14	19*	6
16	45*	17

-10,1,L

1	36*	26
2	81	83
3	24*	30
4	13*	17
5	75	77
6	122	129
7	62	62
8	43*	32
9	17*	11
10	17*	18
11	17*	26
12	19*	11
13	51*	3
14	45*	18
15	32*	4
16	43*	6
17	19*	3

-10,2,L

1	32*	39
2	24*	13
3	13*	1
4	132	125
5	111	115
6	226	228
7	45*	37
8	41*	32
9	39*	0
10	119	128
11	51*	51
12	17*	6
13	19*	2
14	19*	1
15	22*	4
16	49*	1
17	22*	6

-10,3,L

1	158	149
2	70	66
3	141	124
4	126	125
5	211	201
6	309	314
7	39*	47
8	85	100
9	17*	22
10	145	144
11	98	92
12	19*	12
13	19*	19
14	22*	20
15	32*	16
16	22*	12

-10,4,L

1	198	203
2	130	131
3	109	99
4	15*	3
5	15*	6
6	70	67
7	47*	47
8	81	79
9	17*	24
10	66	45
11	17*	16
12	39*	14
13	19*	7
14	32*	4
15	19*	19
16	22*	11

-10,5,L

1	81	76
2	43*	45
3	15*	8
4	58	69
5	15*	8
6	15*	8
7	47*	24
8	51*	25
9	34*	10
10	17*	10
11	19*	0
12	19*	4
13	47*	14
14	19*	8
15	19*	2
16	22*	9

-10,6,L

1	98	94
2	39*	29
3	109	111
4	96	111
5	15*	29
6	32*	19
7	54*	40
8	17*	2
9	51*	58
10	17*	13
11	19*	11
12	54*	15
13	32*	31
14	22*	2
15	19*	5

-10,7,L

1	105	93
2	53	52
3	39*	23
4	60	41
5	70	35
6	17*	1
7	17*	2
8	94	109
9	30*	8
10	19*	5
11	19*	4
12	51*	11
13	22*	11
14	22*	12
15	22*	6

-10,8,L

1	17*	34
2	17*	1
3	45*	56
4	54*	53
5	43*	31
6	17*	6
7	36*	38
8	19*	16
9	19*	20
10	19*	5
11	19*	1
12	56*	9
13	51*	44
14	22*	4

-10,9,L

1	17*	11
2	32*	39
3	128	113
4	49*	47
5	19*	29
6	49*	53
7	19*	21
8	19*	12
9	19*	3
10	19*	23
11	22*	7
12	54*	3
13	36*	16

-10,10,L

1	92	80
2	43*	8
3	139	125
4	64	62
5	34*	7
6	19*	1
7	19*	8
8	19*	15
9	30*	2
10	22*	13
11	22*	1
12	22*	3
13	22*	14

-9,0,L

1	495	487
3	13*	2
5	107	104
7	68	70
9	15*	9
11	47*	55
13	19*	9
15	45*	44
17	41*	1

-9,1,L

1	75	87
2	326	316
3	132	130
4	87	85
5	28*	18
6	81	82
7	15*	6
8	39*	17
9	15*	17
10	55	57
11	68	68

-9,1,L

12	51*	37
13	19*	5
14	19*	1
15	19*	6
16	19*	16
17	22*	4

-9,2,L

1	66	65
2	73	64
3	119	112
4	190	187
5	188	195
6	211	226
7	100	92
8	73	75
9	77	86
10	17*	5
11	98	100
12	19*	1
13	41*	13
14	19*	11
15	19*	7
16	19*	4
17	19*	4

-9,3,L

1	113	101
2	47	45
3	147	145
4	36*	17
5	96	83
6	324	327
7	60	64
8	83	86
9	92	87
10	81	83
11	45*	35
12	51*	5
13	19*	12
14	39*	1
15	19*	12
16	19*	10
17	43*	0

-9,4,L

1	337	336
2	24*	26
3	15*	15
4	36*	19
5	49*	45
6	47*	32
7	15*	45
8	75	58
9	39*	3
10	34*	13
11	19*	25
12	19*	2
13	19*	23
14	19*	1
15	47*	7
16	19*	11

-9,5,L

1	77	86
2	41*	24
3	70	75
4	32*	5
5	32*	20
6	26*	25
7	15*	1
8	47*	38
9	39*	33
10	17*	6
11	19*	2
12	19*	3
13	19*	12
14	19*	2
15	22*	10
16	22*	2

-9,6,L

1	15*	42
2	83	89
3	171	175
4	194	202
5	30*	9
6	30*	21
7	39*	29
8	49*	42
9	58	27
10	19*	8
11	45*	15
12	19*	1
13	19*	16
14	19*	10
15	19*	2

-9,7,L

1	41*	2
2	34*	10
3	39*	4
4	49*	38
5	15*	6
6	60	70
7	17*	4
8	56*	57
9	62	27
9	34*	27
10	19*	16
11	19*	1
12	19*	11
13	34*	6
14	19*	17
15	22*	12

-9,8,L

1	128	121
2	92	84
3	79	79
4	26*	14
5	30*	21
6	17*	14
7	19*	15
8	19*	45
9	19*	21
10	28*	4
11	19*	8
12	22*	11
13	56*	53
14	22*	20

-9,9,L

1	17*	13
2	30*	31
3	30*	36
4	19*	1
5	19*	31
6	34*	8
7	19*	8
8	19*	3
9	19*	22
10	19*	11
11	22*	19
12	22*	23
13	22*	14
14	22*	23

-9,10,L

1	51*	52
2	113	91
3	68	40
4	47*	51
5	45*	6
6	32*	20
7	41*	3
8	19*	2
9	22*	17
10	22*	15
11	22*	6
12	22*	17
13	30*	21

-8,0,L

2	30*	30
4	77	80
6	58	48
8	77	66
10	24*	11
12	28*	24
14	32*	3
16	22*	34

-8,1,L

1	22*	20
2	85	71
3	284	277
4	269	270
5	15*	11
6	94	87
7	15*	3
8	26*	31
9	17*	7
10	55	43
11	47*	27
12	17*	7
13	34*	7
14	36*	4
15	19*	23
16	19*	2
17	32*	4

-8,2,L

1	68	65
2	117	109
3	228	223
4	508	494
5	139	142
6	203	200
7	45*	51
8	15*	28
9	24*	30
10	55	34
11	17*	25
12	19*	30

-8,2,L

13	19*	18
14	19*	12
15	19*	9
16	22*	4
17	22*	2

-8,3,L

1	81	79
2	205	194
3	43*	49
4	24*	14
5	24*	3
6	222	220
7	26*	30
8	258	265
9	143	146
10	17*	6
11	19*	9
12	19*	28
13	19*	1
14	28*	15
15	19*	17
16	39*	12
17	19*	4

-8,4,L

1	39*	24
2	43*	36
3	109	107
4	132	126
5	49*	39
6	75	64
7	43*	8
8	98	97
9	83	98
10	17*	21
11	34*	17
12	30*	18
13	19*	38
14	19*	18
15	30*	23
16	36*	20

-8,5,L

1	62	63
2	53	57
3	66	72
4	68	66
5	62	64
6	15*	12
7	49*	52
8	17*	8
9	36*	14
10	58*	28
11	32*	62
12	45*	18
13	54*	20
14	32*	12
15	41*	14
16	19*	11

-8,6,L

1	41*	30
2	39*	39
3	55	69
4	177	186
5	36*	20
6	68	85
7	17*	24
8	28*	46
9	54*	11
10	19*	42
11	32*	27
12	19*	3
13	19*	1
14	19*	9
15	36*	1
16	47*	3

-8,7,L

1	147	154
2	77	75
3	34*	9
4	39*	13
5	36*	10
6	100	106
7	17*	17
8	79	76
9	36*	20
10	19*	3
11	47*	10
12	43*	5
13	36*	1
14	22*	6
15	49*	10

-8,8,L

1	264	262
2	154	150
3	51*	33
4	17*	34
5	17*	8
6	45*	30
7	17*	10
8	45*	42
9	19*	25
10	19*	20
11	43*	26
12	43*	4
13	39*	28
14	22*	30

-8,9,L

1	60	43
2	49*	34
3	17*	18
4	70	44
5	58*	62
6	19*	9
7	19*	9
8	47*	6
9	34*	2
10	47*	17
11	22*	26
12	22*	12
13	49*	47
14	45*	4

-8,10,L

1	117	91
2	94	74
3	79	62
4	41*	40
5	43*	12
6	30*	3
7	19*	1
8	19*	4
9	19*	3
10	19*	9
11	22*	7
12	22*	2
13	22*	8

-7,0,L

1	166	172
3	109	102
5	232	235
7	15*	2
9	34*	34
11	17*	1
13	32*	37
15	19*	15
17	62*	1

-7,1,L

1	215	212
2	55	61
3	241	244
4	196	189
5	39*	30
6	137	126
7	39*	43
8	73	71
9	75	66
10	41*	34
11	55	19
12	19*	19
13	45*	18
14	47*	24
15	19*	7
16	54*	9
17	22*	1

-7,2,L

1	11*	3
2	90	87
3	503	489
4	469	465
5	64	70
6	15*	35
7	15*	40
8	45*	25
9	17*	4
10	43*	12
11	26*	16
12	19*	25
13	43*	28
14	68	4
15	19*	2
16	45*	7
17	22*	8

-7,3,L

1	13*	13
2	100	89
3	245	241
4	218	211
5	15*	17
6	15*	34
7	43*	45
8	190	193
9	171	173
10	30*	14
11	19*	19
12	47*	2

-7,3,L

13	19*	9
14	19*	5
15	43*	5
16	49*	21
17	39*	15

-7,4,L

1	109	102
2	68	64
3	28*	42
4	15*	22
5	15*	26
6	26*	24
7	17*	32
8	122	133
9	113	126
10	17*	17
11	75	58
12	34*	10
13	19*	7
14	45*	32
15	39*	27
16	22*	26

-7,5,L

1	83	90
2	15*	7
3	49	16
4	30*	16
5	36*	6
6	126	124
7	75	70
8	34*	15
9	17*	23
10	32*	29
11	19*	31
12	19*	6
13	47*	25
14	19*	16
15	19*	3
16	30*	16

-7,6,L

1	126	126
2	66	72
3	45*	28
4	15*	26
5	70	49
6	64	72
7	68	71
8	39*	9
9	17*	3
10	17*	1
11	19*	17
12	19*	5
13	39*	13
14	19*	9
15	22*	2
16	22*	0

-7,7,L

1	66	64
2	166	181
3	39*	58
4	58	55
5	28*	9
6	17*	12
7	81	83
8	28*	19
9	43*	18
10	19*	16
11	19*	2
12	19*	16
13	22*	7
14	19*	3
15	45*	5

-7,8,L

1	145	131
2	147	138
3	34*	22
4	83	68
5	17*	3
6	85	81
7	34*	32
8	17*	2
9	34*	2
10	19*	4
11	19*	7
12	41*	24
13	34*	7
14	22*	14

-7,9,L

1	17*	18
2	54*	23
3	32*	29
4	17*	1
5	60	51
6	36*	7
7	17*	9
8	19*	7
9	19*	5
10	58*	35
11	54*	31
12	22*	13
13	49*	12
14	22*	3

-7,10,L

1	54*	38
2	39*	34
3	28*	30
4	56*	31
5	51*	12
6	19*	24
7	19*	10
8	19*	23
9	19*	8
10	36*	10
11	58*	28
12	34*	5
13	22*	6

-6,0,L

2	19*	17
4	130	126
6	34*	45
8	158	154
10	81	84
12	45*	21
14	19*	38
16	22*	7

-6,1,L

1	166	162
2	11*	12
3	352	343
4	403	398
5	232	237
6	102	104
7	53	57
8	73	68
9	169	166
10	17*	19
11	32*	20
12	17*	0
13	34*	35
14	19*	34
15	19*	1
16	22*	2
17	22*	3

-6,2,L

1	11*	21
2	403	390
3	288	271
4	800	786
5	205	206
6	126	124
7	49*	51
8	15*	16
9	17*	28
10	17*	30
11	17*	4
12	41*	46
13	19*	27
14	45*	1
15	19*	13
16	22*	4
17	22*	1

-6,3,L

1	66	62
2	388	383
3	51	48
4	34*	44
5	26*	21
6	70	65
7	43*	51
8	28*	28
9	128	116
10	17*	12
11	17*	12
12	17*	23
13	19*	4
14	19*	6
15	22*	18
16	22*	18
17	22*	2

-6,4,L

1	352	356
2	55	53
3	94	87
4	15*	4
5	26*	28
6	156	151
7	85	87
8	143	144
9	96	92
10	17*	12
11	17*	19
12	28*	17
13	19*	8

-6,4,L

14	19*	1
15	22*	7
16	51*	13

-6,5,L

1	100	91
2	15*	9
3	58	68
4	15*	23
5	75	72
6	87	82
7	15*	16
8	17*	14
9	60	39
10	43*	10
11	54*	58
12	41*	16
13	36*	40
14	30*	9
15	43*	0
16	51*	2

-6,6,L

1	45*	57
2	15*	35
3	15*	16
4	124	125
5	17*	36
6	55	61
7	58	41
8	17*	15
9	41*	20
10	19*	5
11	19*	20
12	19*	9
13	19*	5
14	32*	8
15	32*	2
16	22*	6

-6,7,L

1	179	188
2	171	196
3	39*	19
4	41*	27
5	53	33
6	62	52
7	58	49
8	17*	24
9	19*	5
10	19*	10
11	28*	1
12	19*	8
13	19*	0
14	19*	8
15	22*	2

-6,8,L

1	81	59
2	43*	36
3	47*	24
4	34*	6
5	17*	28
6	124	120
7	56*	19
8	19*	4
9	19*	27
10	19*	2
11	43*	32
12	39*	44
13	22*	11
14	22*	3

-6,9,L

1	36*	28
2	92	58
3	45*	5
4	56*	45
5	19*	23
6	54*	4
7	49*	25
8	19*	11
9	19*	20
10	19*	3
11	134	115
12	22*	14
13	22*	2
14	22*	6

-6,10,L

1	39*	11
2	19*	12
3	28*	27
4	28*	3
5	19*	15
6	36*	33
7	19*	33
8	45*	16
9	19*	19
10	22*	17
11	70	11
12	22*	25
13	22*	10

-5,0,L

1	1143	1155
3	151	146
5	132	131
7	45*	24
9	169	175
11	58	45
13	39*	35
15	19*	3
17	22*	3

-5,1,L

1	70	69
2	386	379
3	85	88
4	352	344
5	13*	14
6	15*	9
7	51	48
8	15*	25
9	17*	31
10	41*	12
11	17*	1
12	34*	22
13	54*	48
14	39*	30
15	30*	1
16	70	2
17	32*	2

-5,2,L

1	113	117
2	79	92
3	58	60
4	595	589
5	64	59
6	96	97
7	47*	51
8	15*	13
9	43*	51
10	17*	1
11	17*	24
12	19*	3
13	19*	22
14	32*	0
15	22*	7
16	22*	10
17	22*	1

-5,3,L

1	572	560
2	262	248
3	45	40
4	53	58
5	58	47
6	15*	3
7	92	105
8	15*	25
9	26*	16
10	17*	26
11	19*	32
12	19*	10
13	51*	36
14	58*	45
15	22*	5
16	22*	1
17	22*	4

-5,4,L

1	79	76
2	22*	23
3	87	81
4	92	80
5	15*	31
6	354	351
7	256	269
8	81	67
9	100	92
10	17*	15
11	41*	13
12	19*	24
13	19*	41
14	19*	30
15	22*	6
16	22*	5

-5,5,L

1	162	153
2	102	104
3	111	111
4	28*	36
5	122	121
6	70	66
7	75	71
8	51*	63
9	17*	8
10	17*	18
11	54*	32
12	19*	36
13	19*	11
14	19*	2

-5,5,L

15	19*	4
16	22*	2

-5,6,L

1	58	44
2	36*	28
3	32*	34
4	119	114
5	39*	32
6	51*	43
7	26*	2
8	49*	17
9	45*	26
10	17*	19
11	19*	15
12	34*	14
13	19*	8
14	19*	6
15	22*	2
16	19*	11

-5,7,L

1	47*	64
2	175	176
3	32*	44
4	15*	19
5	26*	27
6	17*	21
7	34*	29
8	32*	1
9	19*	22
10	19*	20
11	32*	4
12	19*	16
13	30*	5
14	45*	6
15	58*	9

-5,8,L

1	49*	44
2	70	67
3	36*	22
4	60	57
5	17*	6
6	79	65
7	43*	40
8	17*	12
9	19*	13
10	19*	7
11	36*	21
12	19*	9
13	22*	22
14	49*	9
15	36*	12

-5,9,L

1	17*	19
2	51*	25
3	30*	8
4	51*	15
5	41*	2
6	56*	53
7	30*	17
8	19*	5
9	19*	8
10	19*	4
11	22*	25
12	22*	51
13	22*	9
14	19*	4

-5,10,L

1	28*	2
2	66	62
3	45*	44
4	45*	26
5	19*	14
6	41*	22
7	19*	9
8	36*	25
9	39*	21
10	19*	24
11	75	47
12	54*	5
13	22*	3

-4,0,L

2	17*	12
4	335	344
6	188	192
8	92	91
10	34*	39
12	28*	17
14	60	20
16	30*	4

-4,1,L

1	503	504
2	1231	1233
3	41	33
4	173	169
5	81	67
6	13*	5
7	15*	16
8	15*	5
9	32*	26
10	49*	3
11	17*	26
12	19*	18
13	19*	8
14	19*	12
15	19*	2
16	19*	6
17	22*	3

-4,2,L

1	222	223
2	328	310
3	11*	5
4	36*	33
5	34*	41
6	26*	15
7	62	68
8	45*	31
9	15*	9
10	36*	7
11	45*	52
12	56*	34
13	19*	10
14	51*	46
15	45*	17
16	22*	23
17	51*	5

-4,3,L

1	260	258
2	403	391
3	53	48
4	85	92
5	70	60
6	130	133
7	15*	9
8	15*	19
9	60	63
10	77	68
11	34*	14
12	43*	21
13	54*	50
14	56*	57
15	54*	18
16	22*	13
17	77	6

-4,4,L

1	64	53
2	43	47
3	19*	15
4	58	59
5	55	50
6	273	272
7	333	333
8	60	59
9	90	83
10	56*	37
11	19*	24
12	19*	1
13	58*	9
14	43*	28
15	19*	24
16	32*	3

-4,5,L

1	15*	10
2	24*	43
3	92	91
4	207	198
5	62	51
6	111	118
7	156	161
8	15*	11
9	94	93
10	45*	7
11	62	47
12	45*	43
13	19*	1
14	19*	1
15	22*	3
16	30*	4

-4,6,L

1	32*	39
2	134	138
3	15*	1
4	207	210
5	126	130
6	58	47
7	17*	16
8	17*	28
9	19*	26
10	36*	33
11	62	42
12	19*	19
13	19*	15
14	19*	9
15	22*	7

-4,6,L			14	19*	4	5	36*	32	-3,5,L		
						6	141	146			
16	22*	8	-4,10,L			7	143	148	1	13*	10
						8	73	54	2	24*	8
-4,7,L			1	45*	30	9	30*	15	3	62	45
			2	17*	6	10	17*	9	4	26*	32
1	98	84	3	60*	59	11	58	57	5	134	120
2	15*	12	4	49*	27	12	54*	49	6	211	223
3	36*	30	5	49*	10	13	43*	19	7	85	67
4	34*	23	6	17*	19	14	19*	37	8	17*	18
5	17*	11	7	19*	29	15	41*	1	9	43*	26
6	30*	25	8	43*	26	16	19*	10	10	36*	35
7	17*	7	9	81	66	17	22*	20	11	41*	9
8	43*	46	10	22*	7				12	19*	29
9	19*	21	11	47*	30	-3,3,L			13	19*	5
10	41*	10	12	22*	0				14	41*	8
11	19*	12	13	22*	7	1	75	78	15	22*	8
12	19*	15				2	81	89	16	43*	0
13	19*	4	-3,0,L			3	87	87			
14	22*	8				4	119	131	-3,6,L		
15	22*	7	1	520	527	5	79	82			
			3	390	379	6	51	34	1	39*	42
-4,8,L			5	147	143	7	36*	15	2	15*	1
			7	476	486	8	28*	1	3	15*	0
1	15*	1	9	70	57	9	15*	16	4	94	89
2	62	50	11	30*	10	10	60	63	5	58	49
3	62	47	13	19*	7	11	19*	29	6	15*	12
4	17*	34	15	19*	4	12	19*	29	7	66	55
5	111	104	17	22*	2	13	41*	33	8	39*	7
6	17*	4				14	32*	20	9	17*	17
7	17*	5	-3,1,L			15	19*	4	10	17*	16
8	19*	13				16	56*	25	11	79	58
9	68	53	1	659	672	17	30*	19	12	32*	12
10	19*	5	3	612	601				13	28*	7
11	34*	18	4	162	164	-3,4,L			14	19*	5
12	32*	6	5	162	168				15	22*	5
13	19*	6	6	15*	32	1	151	155	16	22*	8
14	54*	2	7	134	127	2	156	154			
15	22*	6	8	75	79	3	39*	34	-3,7,L		
			9	15*	21	4	43*	38			
-4,9,L			10	26*	14	5	132	134	1	15*	24
			11	94	77	6	107	101	2	36*	34
1	55	24	12	19*	28	7	43*	53	3	15*	9
2	17*	7	13	19*	10	8	17*	17	4	15*	25
3	17*	19	14	19*	5	9	32*	38	5	66	78
4	47*	42	15	45*	1	10	17*	33	6	68	58
5	19*	46	16	34*	1	11	17*	20	7	39*	57
6	17*	21	17	22*	5	12	34*	9	8	47*	17
7	17*	7				13	30*	4	9	77	58
8	19*	19	-3,2,L			14	39*	12	10	79	39
9	58*	46				15	22*	2	11	19*	3
10	19*	25	1	143	140	16	22*	11	12	49*	3
11	22*	26	2	147	131				13	19*	12
12	47*	14	3	149	135				14	19*	4
13	22*	4	4	13*	4				15	22*	4

-3,8,L

1	15*	13
2	28*	11
3	17*	35
4	15*	13
5	66	66
6	43*	42
7	51*	29
8	45*	30
9	83	81
10	32*	46
11	19*	0
12	36*	13
13	22*	0
14	22*	17
15	22*	2

-3,9,L

1	17*	18
2	17*	7
3	17*	12
4	190	170
5	39*	2
6	19*	1
7	19*	11
8	19*	7
9	19*	43
10	75	60
11	19*	33
12	22*	12
13	22*	8
14	22*	1

-3,10,L

1	17*	13
2	19*	43
3	30*	29
4	45*	44
5	19*	35
6	32*	4
7	43*	0
8	19*	26
9	105	93
10	68	36
11	22*	0
12	22*	8
13	22*	2

-2,0,L

2	1325	1292
4	245	248
6	43*	32
8	15*	21
10	26*	25
12	17*	1
14	19*	3
16	19*	3

-2,1,L

1	30	26
2	1258	1262
3	47	61
4	105	109
5	160	163
6	200	194
7	98	93
8	51	54
9	77	76
10	55	39
11	17*	7
12	41*	13
13	19*	3
14	19*	9
15	19*	1
16	19*	7
17	28*	8

-2,2,L

1	232	235
2	177	173
3	399	394
4	53	58
5	77	74
6	15*	13
7	34*	17
8	32*	24
9	15*	3
10	17*	18
11	43*	4
12	107	124
13	19*	6
14	19*	9
15	56*	2
16	43*	13
17	22*	10

-2,3,L

1	380	385
2	350	340
3	13*	18
4	34*	29
5	43*	0
6	81	81
7	198	201
8	55	53
9	15*	15
10	17*	17
11	73	63
12	39*	42
13	32*	6
14	47*	30
15	36*	5
16	22*	35
17	58*	20

-2,4,L

1	62	57
2	117	115
3	55	54
4	32*	15
5	92	103
6	119	123
7	81	71
8	28*	6
9	17*	6
10	17*	5
11	30*	9
12	17*	9
13	19*	18
14	30*	7
15	22*	5
16	22*	23

-2,5,L

1	36*	12
2	341	328
3	190	189
4	435	448
5	363	373
6	68	61
7	32*	7
8	32*	30
9	17*	18
10	34*	24
11	66	36
12	19*	4
13	19*	12
14	19*	1
15	34*	4
16	19*	3

-2,6,L

1	36*	39
2	49	40
3	87	79
4	53	50
5	77	67
6	15*	14
7	98	92
8	17*	3
9	79	56
10	51*	37
11	36*	31
12	43*	8
13	19*	11
14	22*	14
15	22*	12
16	43*	5

-2,7,L

1	32*	18
2	32*	24
3	28*	9
4	15*	13
5	26*	15
6	26*	7
7	32*	9
8	39*	6
9	56*	61
10	19*	14
11	47*	33
12	19*	1
13	19*	2
14	22*	26
15	22*	1

-2,8,L

1	15*	4
2	49*	50
3	17*	16
4	30*	41
5	36*	21
6	28*	36
7	19*	39
8	32*	23
9	58*	51
10	19*	42
11	19*	2
12	19*	2
13	41*	7
14	43*	13
15	22*	10

-2,9,L

1	17*	4
2	17*	19

-2,9,L

3	47*	40
4	64	47
5	73	65
6	17*	19
7	34*	17
8	19*	3
9	19*	9
10	32*	3
11	49*	17
12	45*	2
13	30*	20
14	32*	2

-2,10,L

1	17*	12
2	58	3
3	17*	7
4	54*	59
5	19*	17
6	19*	16
7	17*	16
8	19*	1
9	96	86
10	87	45
11	19*	3
12	22*	4
13	54*	1

-1,0,L

1	275	268
3	382	380
5	58	52
7	15*	16
9	15*	18
11	17*	26
13	19*	0
15	19*	5
17	41*	15

-1,1,L

1	346	350
2	87	89
3	75	77
4	60	63
5	252	235
6	60	54
7	141	145
8	39*	38
9	15*	20
10	49*	21
11	17*	14
12	70	78
13	19*	18
14	34*	8
15	22*	9
16	19*	12
17	22*	9

-1,2,L

1	350	356
2	70	62
3	81	83
4	254	263
5	13*	6
6	81	79
7	68	76
8	22*	37
9	66	75
10	17*	39
11	117	115
12	87	85
13	19*	23
14	34*	12
15	19*	14
16	58*	6
17	22*	16

-1,3,L

1	70	72
2	87	76
3	22*	4
4	24*	17
5	188	188
6	15*	19
7	147	158
8	32*	45
9	28*	31
10	70	65
11	26*	6
12	58*	67
13	19*	21
14	19*	20
15	36*	16
16	22*	21
17	22*	9

-1,4,L

1	149	145
2	205	198
3	119	118
4	186	179
5	77	85
6	15*	7
7	145	149
8	105	90
9	60	66
10	17*	13
11	28*	1
12	19*	13
13	19*	15
14	19*	7
15	19*	3
16	22*	10

-1,5,L

1	51	45
2	286	282
3	166	169
4	301	316
5	431	430
6	30*	3
7	15*	27
8	53	33
9	17*	16
10	17*	4
11	30*	37
12	49*	6
13	19*	16
14	19*	5
15	22*	5
16	19*	3

-1,6,L

1	24*	14
2	26*	4
3	102	105
4	181	173
5	102	100
6	85	83
7	36*	29
8	30*	27
9	77	70
10	98	78
11	19*	1
12	19*	10
13	19*	1
14	22*	3
15	47*	3
16	22*	1

-1,7,L

1	64	73
2	117	121
3	126	129
4	34*	12
5	15*	20
6	28*	2
7	68	38
8	43*	7
9	45*	30
10	62	28
11	19*	13
12	19*	26
13	39*	6
14	22*	14
15	22*	8

-1,8,L

1	43*	1
2	34*	32
3	17*	22
4	17*	33
5	51*	32
6	17*	10
7	54*	49
8	19*	18
9	54*	42
10	19*	10
11	45*	14
12	47*	3
13	45*	7
14	22*	19

-1,9,L

1	17*	20
2	119	119
3	60	45
4	17*	21
5	17*	26
6	28*	7
7	30*	1
8	43*	3
9	41*	7
10	19*	15
11	34*	3
12	22*	12
13	30*	12
14	22*	6

-1,10,L

1	28*	4
2	77	64
3	17*	19
4	19*	29
5	19*	15

-1,10,L

6	49*	13
7	19*	7
8	70	43
9	22*	14
10	34*	28
11	22*	11
12	34*	6
13	22*	4

0,0,L

2	205	218
4	134	132
6	79	80
8	45*	15
10	34*	3
12	19*	20
14	19*	2
16	22*	13

0,1,L

1	158	157
2	196	196
3	58	55
4	70	63
5	544	539
6	39*	44
7	98	88
8	51	41
9	58	56
10	17*	1
11	45*	25
12	54*	54
13	19*	12
14	19*	13
15	19*	4
16	19*	8
17	22*	5

0,2,L

0	424	447
1	139	146
2	85	85
3	290	278
4	224	222
5	171	168
6	68	63
7	66	55
8	15*	12
9	17*	28
10	113	110
11	54*	64
12	73	66
13	36*	10
14	19*	13
15	19*	11
16	22*	13
17	51*	5

0,3,L

1	179	173
2	26*	19
3	60	55
4	22*	12
5	47	41
6	75	75
7	81	77
8	15*	16
9	17*	42
10	98	91
11	17*	13
12	19*	29
13	19*	3
14	19*	35
15	30*	20
16	22*	6
17	41*	0

0,4,L

0	122	112
1	79	72
2	322	331
3	34*	18
4	45*	52
5	149	156
6	43*	33
7	49	47
8	87	89
9	17*	15
10	17*	24
11	47*	2
12	19*	27
13	43*	10
14	45*	50
15	22*	30
16	32*	4

0,5,L

1	115	115
2	49	49
3	102	119
4	203	209
5	151	161
6	36*	34
7	30*	20
8	30*	8
9	39*	10
10	49*	21
11	19*	8
12	28*	15
13	47*	13
14	19*	13
15	19*	13
16	22*	2

0,6,L

0	171	167
1	15*	16
2	162	171
3	15*	25
4	209	208
5	15*	25
6	47*	39
7	47*	45
8	54*	49
9	17*	10
10	19*	33
11	19*	14
12	19*	21
13	19*	18
14	19*	1
15	22*	1
16	22*	5

0,7,L

1	15*	15
2	134	133
3	15*	11
4	43*	56
5	58	60
6	77	74
7	158	162
8	94	101
9	49*	61
10	54*	26
11	19*	2
12	68	8
13	19*	7
14	19*	13
15	22*	7

0,8,L

0	17*	10
1	15*	12
2	94	94
3	109	101
4	28*	25
5	17*	11
6	32*	26
7	109	108
8	85	57
9	19*	44
10	19*	9
11	19*	9
12	45*	7
13	19*	3
14	22*	22

0,9,L

1	49*	40
2	32*	45
3	115	117
4	70	75
5	17*	5
6	17*	6
7	32*	0
8	43*	9
9	19*	15
10	19*	16
11	19*	9
12	22*	20
13	22*	6
14	22*	6

0,10,L

0	41*	14
1	17*	2
2	98	86
3	19*	26
4	30*	7
5	19*	4
6	41*	8
7	19*	10
8	62*	47
9	22*	36
10	19*	5
11	22*	11
12	22*	2
13	62*	3

1,0,L

1	815	824
3	194	202
5	250	252
7	60	65
9	111	103

1,0,L

11	17*	8
13	19*	19
15	34*	11
17	22*	3

1,1,L

0	378	393
1	435	452
2	198	201
3	181	186
4	241	228
5	235	222
6	115	123
7	15*	17
8	15*	11
9	81	80
10	113	106
11	17*	9
12	19*	10
13	43*	8
14	19*	11
15	30*	8
16	30*	1
17	58*	2

1,2,L

0	350	377
1	132	143
2	11*	5
3	179	177
4	235	220
5	36*	31
6	117	117
7	81	76
8	15*	21
9	107	106
10	62	56
11	17*	2
12	36*	21
13	51*	3
14	41*	8
15	49*	5
16	22*	7
17	34*	4

1,3,L

0	17*	1
1	115	125
2	81	82
3	75	79
4	232	220
5	288	269
6	64	55
7	41*	53
8	30*	35
9	124	122
10	83	87
11	39*	23
12	19*	13
13	43*	20
14	19*	24
15	34*	35
16	22*	8
17	51*	8

1,4,L

0	599	604
1	205	215
2	105	101
3	73	81
4	47	32
5	79	66
6	15*	14
7	36*	28
8	81	85
9	26*	35
10	28*	6
11	17*	3
12	19*	18
13	34*	14
14	56*	54
15	30*	33
16	47*	1

1,5,L

0	100	86
1	13*	5
2	47	43
3	173	175
4	81	91
5	41*	45
6	15*	1
7	30*	24
8	15*	22
9	28*	24
10	28*	10
11	19*	11
12	28*	22
13	49*	23
14	41*	27
15	41*	16
16	51*	10

1,6,L

0	75	72
1	15*	17
2	286	301
3	378	387
4	30*	39
5	79	83
6	47*	52
7	66	62
8	17*	13
9	68	65
10	19*	14
11	39*	20
12	19*	26
13	19*	0
14	19*	7
15	22*	3

1,7,L

0	58	55
1	64	53
2	15*	20
3	73	67
4	53	44
5	36*	41
6	45*	15
7	70	67
8	105	98
9	54*	43
10	28*	14
11	19*	4
12	36*	13
13	19*	15
14	54*	6
15	22*	5

1,8,L

0	94	89
1	70	65
2	58	33
3	17*	33
4	36*	15
5	17*	11
6	64	45
7	19*	51
8	17*	2
9	19*	12
10	19*	30
11	19*	2
12	41*	25
13	19*	6
14	22*	0

1,9,L

0	47*	48
1	17*	14
2	79	73
3	45*	24
4	17*	24
5	17*	21
6	17*	3
7	17*	25
8	19*	8
9	45*	20
10	51*	11
11	43*	2
12	34*	23
13	47*	5
14	22*	5

1,10,L

0	17*	1
1	17*	23
2	92	97
3	49*	30
4	32*	3
5	17*	6
6	43*	2
7	36*	2
8	19*	9
9	22*	20
10	19*	4
11	39*	15
12	22*	10
13	56*	0

2,0,L

0	619	643
2	269	277
4	181	180
6	132	134
8	55	53
10	158	151
12	30*	35
14	62*	45
16	22*	12

2,1,L

0	523	555
1	644	658
2	188	188
3	22*	9

2,1,L

4	186	176
5	70	57
6	126	125
7	43*	46
8	30*	35
9	132	130
10	179	187
11	30*	39
12	54*	13
13	19*	7
14	36*	1
15	34*	30
16	19*	5
17	19*	1

2,2,L

0	299	307
1	311	322
2	11*	3
3	358	358
4	39*	31
5	486	476
6	122	108
7	66	71
8	43*	47
9	32*	27
10	151	141
11	56*	25
12	19*	19
13	19*	9
14	19*	6
15	19*	4
16	22*	12
17	22*	3

2,3,L

0	292	298
1	314	313
2	177	187
3	158	163
4	66	60
5	303	298
6	49	45
7	45*	50
8	92	82
9	39*	40
10	32*	20
11	41*	20
12	19*	32
13	19*	9
14	19*	16
15	39*	11
16	22*	3

2,4,L

0	273	268
1	369	357
2	132	135
3	117	109
4	137	136
5	15*	4
6	15*	22
7	15*	21
8	64	70
9	49*	33
10	36*	16
11	19*	7
12	58*	30
13	58*	10
14	22*	31
15	19*	24
16	19*	3

2,5,L

0	126	129
1	39*	35
2	107	99
3	62	76
4	139	145
5	62	70
6	49*	48
7	60	59
8	39*	54
9	32*	1
10	17*	20
11	32*	7
12	36*	25
13	22*	5
14	22*	19
15	22*	6
16	39*	1

2,6,L

0	49	38
1	128	124
2	378	389
3	390	405
4	15*	2
5	39*	22
6	64	65
7	36*	45
8	30*	30
9	17*	29
10	28*	41
11	54*	21
12	41*	11
13	22*	6
14	19*	5
15	22*	7

2,7,L

0	15*	26
1	90	84
2	98	105
3	39*	35
4	15*	1
5	205	181
6	62	36
7	147	147
8	90	79
9	19*	40
10	51*	5
11	19*	1
12	36*	11
13	19*	6
14	22*	7
15	58*	2

2,8,L

0	47*	59
1	15*	21
2	43*	28
3	36*	27
4	15*	31
5	49*	33
6	17*	22
7	56*	52
8	19*	25
9	19*	19
10	19*	18
11	36*	12
12	60*	32
13	22*	9
14	34*	2

2,9,L

0	64	45
1	36*	8
2	17*	4
3	43*	0
4	17*	3
5	17*	30
6	17*	0
7	43*	10
8	19*	27
9	19*	2
10	22*	7
11	19*	6
12	22*	14
13	34*	20
14	19*	1

2,10,L

0	30*	37
1	64	53
2	19*	3
3	30*	23
4	51*	4
5	19*	18
6	19*	9
7	39*	33
8	19*	0
9	19*	0
10	19*	19
11	36*	26
12	62*	13
13	22*	9

3,0,L

1	243	244
3	228	219
5	53	66
7	169	173
9	49*	39
11	34*	27
13	19*	12
15	19*	27
17	22*	3

3,1,L

0	239	248
1	51	62
2	480	484
3	70	69
4	100	89
5	58	64
6	28*	7
7	83	80
8	73	76
9	113	116
10	96	104
11	49*	33
12	34*	15
13	36*	13
14	19*	7
15	22*	3

3,1,L

16	19*	12
17	22*	0

3,2,L

0	126	141
1	224	230
2	320	319
3	279	269
4	13*	24
5	62	51
6	34*	17
7	87	101
8	15*	20
9	28*	33
10	54*	42
11	19*	13
12	45*	14
13	51*	23
14	19*	13
15	22*	6
16	22*	4
17	54*	0

3,3,L

0	420	421
1	196	206
2	262	265
3	13*	0
4	77	82
5	15*	14
6	60	58
7	109	116
8	64	82
9	17*	2
10	26*	25
11	17*	16
12	19*	0
13	19*	26
14	43*	27
15	19*	8
16	22*	2

3,4,L

0	196	201
1	73	76
2	47	42
3	94	81
4	15*	22
5	41*	34
6	41*	27
7	85	75
8	128	122
9	17*	3
10	47*	29
11	19*	3
12	58*	57
13	64*	51
14	47*	14
15	22*	12
16	39*	1

3,5,L

0	36*	19
1	164	166
2	115	101
3	166	165
4	115	121
5	47*	31
6	109	113
7	26*	27
8	17*	16
9	17*	18
10	34*	7
11	19*	1
12	81	58
13	51*	36
14	22*	3
15	19*	1
16	22*	5

3,6,L

0	32*	36
1	30*	9
2	115	116
3	260	271
4	81	67
5	207	203
6	124	125
7	54*	49
8	17*	3
9	39*	8
10	19*	35
11	34*	13
12	19*	13
13	60*	20
14	19*	6
15	19*	12

3,7,L

0	175	176
1	32*	9
2	111	111
3	51	66
4	15*	17
5	162	162
6	70	87
7	36*	28
8	73	68
9	28*	1
10	41*	0
11	43*	14
12	19*	3
13	19*	3
14	54*	4
15	22*	1

3,8,L

0	205	220
1	96	104
2	64	71
3	34*	21
4	30*	15
5	17*	15
6	28*	32
7	43*	39
8	19*	26
9	19*	19
10	36*	1
11	41*	3
12	19*	16
13	22*	14
14	22*	1

3,9,L

0	17*	4
1	17*	21
2	17*	2
3	17*	13
4	17*	24
5	41*	34
6	17*	17
7	36*	29
8	19*	6
9	19*	9
10	19*	13
11	19*	4
12	22*	31
13	43*	7

3,10,L

0	58*	46
1	66	61
2	75	56
3	19*	37
4	17*	4
5	19*	2
6	19*	20
7	19*	8
8	34*	42
9	19*	8
10	22*	18
11	22*	12
12	22*	1
13	22*	2

4,0,L

0	45	62
2	318	306
4	346	345
6	26*	9
8	260	259
10	28*	37
12	43*	41
14	19*	4
16	19*	4

4,1,L

0	11*	22
1	107	108
2	222	221
3	456	458
4	13*	1
5	13*	22
6	36*	19
7	15*	21
8	143	136
9	17*	24
10	77	81
11	47*	48
12	41*	20
13	32*	1
14	19*	12
15	39*	0
16	56*	3
17	30*	1

4,2,L

0	162	167
1	196	199
2	90	85
3	994	962
4	26*	26
5	109	105
6	15*	30
7	41*	20

4,2,L

8	15*	12
9	68	63
10	17*	30
11	36*	10
12	19*	10
13	19*	25
14	19*	1
15	19*	5
16	56*	5

4,3,L

0	188	192
1	24*	29
2	24*	16
3	224	229
4	64	56
5	107	113
6	15*	19
7	90	95
8	85	82
9	17*	9
10	17*	6
11	17*	5
12	19*	11
13	19*	7
14	56*	10
15	34*	22
16	22*	11

4,4,L

0	94	89
1	51	48
2	149	148
3	85	77
4	68	70
5	15*	7
6	81	80
7	141	149
8	62	69
9	36*	19
10	41*	24
11	64	42
12	54*	35
13	66	53
14	22*	20
15	22*	17
16	22*	3

4;5,L

0	55	47
1	177	179
2	98	92
3	28*	6
4	15*	18
5	98	96
6	156	157
7	28*	28
8	41*	25
9	30*	41
10	70	72
11	58*	44
12	87	75
13	81	51
14	19*	7
15	22*	10
16	47*	3

4,6,L

0	77	80
1	250	250
2	51	36
3	15*	16
4	60	53
5	213	206
6	132	120
7	26*	29
8	17*	21
9	17*	4
10	19*	19
11	62	35
12	19*	23
13	22*	25
14	19*	3
15	22*	11

4,7,L

0	145	137
1	305	307
2	90	78
3	30*	32
4	15*	9
5	85	83
6	17*	13
7	17*	6
8	49*	23
9	43*	17
10	19*	5
11	19*	5
12	19*	17
13	66	10
14	22*	3
15	22*	1

4,8,L

0	41*	55
1	17*	33
2	17*	18
3	122	122
4	17*	10
5	85	78
6	49*	36
7	92	75
8	19*	0
9	19*	13
10	19*	4
11	19*	11
12	19*	3
13	51*	4
14	22*	5

4,9,L

0	39*	27
1	17*	22
2	47*	45
3	17*	1
4	56*	44
5	17*	14
6	19*	4
7	43*	21
8	19*	24
9	19*	21
10	43*	10
11	30*	16
12	19*	2
13	34*	4

4,10,L

0	36*	14
1	17*	6
2	17*	12
3	17*	15
4	51*	0
5	58*	10
6	47*	24
7	19*	11
8	19*	3
9	19*	8
10	22*	26
11	19*	8
12	51*	10

5,0,L

1	388	387
3	154	154
5	28*	10
7	375	372
9	117	118
11	58*	39
13	81	69
15	34*	2

5,1,L

0	64	65
1	117	113
2	320	316
3	245	241
4	290	269
5	102	94
6	64	69
7	132	127
8	301	295
9	17*	34
10	17*	5
11	17*	5
12	51*	37
13	19*	19
14	19*	20
15	34*	3
16	41*	7

5,2,L

0	45	49
1	160	178
2	66	57
3	299	276
4	28*	29
5	15*	12
6	51	34
7	15*	37
8	15*	23
9	49*	30
10	66	46
11	36*	29
12	54*	14
13	19*	16
14	32*	2
15	19*	5
16	19*	1

5,3,L

0	81	77
1	119	111
2	207	203
3	177	174
4	41*	41

5,3,L		
5	143	133
6	36*	35
7	39*	21
8	58	61
9	17*	11
10	60	14
11	54*	30
12	19*	7
13	19*	10
14	39*	13
15	22*	13
16	22*	5

5,4,L		
0	200	191
1	41*	39
2	181	176
3	98	94
4	87	84
5	64	67
6	15*	32
7	58	56
8	55	60
9	17*	18
10	34*	8
11	19*	16
12	19*	15
13	19*	16
14	41*	1
15	19*	2
16	47*	13

5,5,L		
0	13*	11
1	15*	23
2	98	105
3	30*	16
4	15*	11
5	15*	4
6	83	81
7	17*	0
8	36*	41
9	47*	9
10	17*	13
11	19*	5
12	81	57
13	47*	32
14	22*	9
15	22*	1
16	36*	3

5,6,L		
0	96	94
1	51	72
2	60	51
3	288	275
4	105	104
5	177	179
6	39*	16
7	47*	16
8	28*	11
9	28*	3
10	19*	2
11	19*	24
12	19*	16
13	19*	4
14	22*	4
15	22*	11

5,7,L		
0	296	299
1	309	321
2	36*	25
3	24*	32
4	55	52
5	17*	11
6	17*	25
7	68	60
8	17*	6
9	19*	2
10	17*	4
11	19*	9
12	47*	1
13	34*	18
14	22*	2
15	22*	15

5,8,L		
0	15*	27
1	62	61
2	15*	1
3	26*	42
4	17*	1
5	60	51
6	132	111
7	17*	12
8	19*	19
9	19*	1
10	41*	30
11	45*	24
12	19*	0
13	19*	4
14	22*	6

5,9,L		
0	17*	20
1	17*	25
2	51*	17
3	17*	24
4	64	55
5	17*	25
6	49*	53
7	19*	17
8	19*	17
9	19*	1
10	75	58
11	34*	8
12	19*	1
13	51*	5

5,10,L		
0	45*	17
1	41*	13
2	19*	7
3	19*	25
4	43*	16
5	32*	30
6	19*	21
7	19*	6
8	30*	12
9	22*	1
10	34*	18
11	22*	16
12	54*	1

6,0,L		
0	847	850
2	124	120
4	171	161
6	83	96
8	433	442
10	26*	0
12	32*	1
14	47*	23
16	43*	12

6,1,L		
0	83	88
1	282	283
2	75	80
3	288	271
4	32*	20
5	186	184
6	36*	33
7	66	60
8	17*	12
9	17*	7
10	49*	52
11	43*	31
12	19*	18
13	19*	23
14	19*	4
15	19*	6
16	19*	3

6,2,L		
0	346	357
1	26*	31
2	102	99
3	171	160
4	92	85
5	22*	1
6	28*	1
7	15*	18
8	79	63
9	36*	42
10	43*	4
11	17*	1
12	32*	10
13	34*	31
14	19*	3
15	54*	1
16	30*	1

6,3,L		
0	209	209
1	437	444
2	94	100
3	143	132
4	81	69
5	73	81
6	81	79
7	24*	16
8	41*	44
9	26*	31
10	17*	13
11	19*	1
12	51*	16
13	66	37
14	22*	0
15	19*	3
16	22*	1

6,4,L		
0	68	74

6,4,L

1	64	61
2	51	53
3	55	67
4	66	71
5	132	154
6	156	162
7	15*	9
8	17*	11
9	17*	30
10	17*	18
11	19*	35
12	36*	46
13	30*	2
14	19*	1
15	19*	9
16	19*	8

6,5,L

0	139	138
1	126	127
2	149	160
3	188	182
4	230	237
5	73	68
6	53	69
7	30*	27
8	102	86
9	17*	25
10	85	78
11	96	80
12	19*	16
13	19*	0
14	19*	0
15	56*	3

6,6,L

0	64	69
1	15*	29
2	15*	4
3	247	249
4	24*	36
5	70	61
6	43*	28
7	32*	18
8	43*	39
9	17*	3
10	90	73
11	68	47
12	19*	16
13	19*	10
14	22*	3
15	22*	4

6,7,L

0	107	102
1	256	255
2	15*	15
3	45*	32
4	32*	21
5	75	64
6	28*	16
7	39*	32
8	17*	13
9	19*	31
10	41*	5
11	19*	25
12	56*	7
13	22*	19
14	22*	5

6,8,L

0	51*	61
1	15*	28
2	34*	4
3	17*	21
4	28*	27
5	55	31
6	73	51
7	41*	14
8	28*	5
9	47*	4
10	34*	6
11	22*	10
12	32*	3
13	58*	6
14	32*	9

6,9,L

0	17*	35
1	58	60
2	30*	8
3	43*	1
4	36*	12
5	79	71
6	19*	13
7	19*	14
8	30*	16
9	19*	5
10	19*	12
11	22*	21
12	22*	11
13	32*	5

6,10,L

0	32*	2
1	19*	34
2	45*	18
3	19*	44
4	32*	16
5	64	51
6	19*	12
7	30*	8
8	19*	10
9	22*	8
10	34*	24
11	22*	8
12	22*	1

7,0,L

1	311	301
3	188	191
5	303	287
7	92	90
9	68	81
11	30*	6
13	36*	15
15	41*	1

7,1,L

0	196	196
1	687	674
2	109	110
3	160	147
4	43	39
5	49	48
6	154	160
7	87	81
8	17*	34
9	17*	3
10	30*	32
11	66	61
12	19*	22
13	19*	18
14	19*	6
15	32*	1
16	22*	6

7,2,L

0	209	211
1	19*	36
2	36*	19
3	13*	8
4	13*	6
5	24*	23
6	64	70
7	15*	1
8	17*	33
9	60	49
10	17*	15
11	19*	14
12	19*	15
13	47*	26
14	19*	10
15	49*	7
16	22*	2

7,3,L

0	34*	39
1	478	473
2	24*	12
3	68	73
4	98	79
5	43*	36
6	68	61
7	41*	8
8	34*	24
9	17*	1
10	17*	14
11	30*	22
12	41*	26
13	56*	23
14	49*	10
15	19*	12
16	56*	7

7,4,L

0	49	49
1	262	267
2	98	104
3	183	177
4	15*	11
5	98	110
6	111	122
7	28*	37
8	98	94
9	39*	39
10	17*	21
11	19*	23
12	19*	35
13	54*	16
14	22*	13
15	22*	0
16	22*	5

7,5,L

0	15*	13
1	15*	4
2	45*	46
3	341	353
4	113	105
5	96	98
6	122	126
7	15*	1
8	17*	34
9	49*	42
10	58*	49
11	81	85
12	41*	1
13	45*	1
14	19*	4
15	22*	1

7,6,L

0	49*	55
1	111	115
2	30*	17
3	177	177
4	200	205
5	81	80
6	43*	22
7	49*	30
8	32*	29
9	30*	35
10	81	82
11	70	56
12	19*	16
13	19*	15
14	19*	3
15	22*	14

7,7,L

0	15*	1
1	60	47
2	15*	6
3	49*	52
4	17*	11
5	17*	23
6	54*	39
7	54*	36
8	19*	10
9	47*	34
10	19*	15
11	41*	23
12	30*	12
13	22*	2
14	19*	5

7,8,L

0	79	71
1	15*	7
2	15*	31
3	17*	27
4	39*	15
5	17*	9
6	17*	12
7	39*	19
8	39*	31
9	19*	28
10	49*	16
11	45*	13
12	19*	3
13	22*	2
14	22*	9

7,9,L

0	17*	8
1	70	60
2	17*	6
3	49*	49
4	54*	48
5	56*	33
6	51*	16
7	19*	6
8	19*	4
9	41*	19
10	19*	12
11	22*	1
12	22*	0
13	22*	5

7,10,L

0	62	34
1	17*	10
2	36*	34
3	30*	43
4	47*	34
5	32*	12
6	19*	17
7	19*	23
8	43*	24
9	22*	14
10	56*	18
11	22*	2
12	22*	0

8,0,L

0	117	112
2	124	127
4	13*	9
6	653	666
8	73	75
10	49*	8
12	34*	51
14	41*	20
16	22*	7

8,1,L

0	279	279
1	599	582
2	250	235
3	24*	1
4	22*	30
5	117	122
6	277	289
7	145	137
8	39*	41
9	17*	15
10	34*	2
11	70	50
12	19*	17
13	19*	3
14	19*	5
15	19*	2
16	22*	2

8,2,L

0	66	55
1	203	206
2	158	157
3	117	117
4	45*	44
5	160	165
6	149	148
7	36*	39
8	15*	26
9	17*	14
10	58	35
11	68	44
12	19*	17
13	19*	23
14	19*	0
15	51*	2
16	19*	11

8,3,L

0	51	54
1	77	77
2	13*	20
3	34*	29
4	49	42
5	64	52
6	15*	26
7	34*	41
8	17*	9
9	51*	54
10	17*	2
11	19*	20
12	19*	2
13	19*	14
14	19*	4
15	19*	7
16	22*	12

8,4,L

0	98	105
1	51	46
2	124	125
3	79	85
4	92	93
5	15*	33
6	85	94
7	15*	13
8	58	66
9	17*	26
10	28*	12
11	17*	5
12	28*	7
13	19*	3
14	51*	12
15	22*	9

8,5,L

0	39*	20
1	250	251
2	49*	40
3	181	176
4	126	123
5	75	83
6	39*	48
7	17*	8
8	17*	31
9	77	48
10	19*	12
11	19*	24
12	41*	14
13	43*	11
14	45*	21
15	22*	2

8,6,L

0	41*	26
1	68	63
2	62	52
3	24*	46
4	105	109
5	47*	52
6	66	57
7	34*	14
8	17*	42
9	39*	2
10	126	99
11	19*	35
12	19*	3
13	22*	18
14	22*	14
15	22*	0

8,7,L

0	53	61
1	34*	33
2	30*	27
3	15*	4
4	83	82
5	60	50
6	47*	32
7	17*	5
8	19*	26
9	70	52
10	45*	19
11	19*	3
12	19*	17
13	43*	36
14	19*	11

8,8,L

0	15*	2
1	26*	6
2	15*	9
3	17*	10
4	66	82
5	17*	30
6	34*	3
7	19*	25
8	45*	41
9	19*	7
10	19*	3
11	19*	25
12	19*	3
13	22*	14
14	19*	3

8,9,L

0	49*	21
1	17*	21
2	17*	34
3	107	105
4	43*	36
5	17*	13
6	49*	14
7	19*	2
8	19*	20
9	54*	21
10	19*	13
11	19*	0
12	30*	3
13	43*	1

8,10,L

0	17*	15
1	17*	22
2	39*	22
3	17*	6
4	64	56
5	19*	22
6	30*	12
7	19*	7
8	45*	36
9	39*	16
10	41*	5
11	49*	2
12	22*	1

9,0,L

1	576	559
3	94	97
5	79	73
7	15*	19
9	70	72
11	49*	4
13	19*	7
15	22*	1

9,1,L

0	143	144
1	397	384
2	115	115
3	49	30
4	32*	27
5	262	270
6	262	266
7	17*	23
8	17*	33
9	34*	43
10	49*	30
11	47*	52
12	19*	17
13	19*	2
14	32*	9
15	19*	17
16	22*	16

9,2,L

0	243	245
1	55	59
2	205	202
3	111	112
4	124	127
5	51	53
6	39*	10
7	26*	22
8	51*	46
9	17*	3
10	85	80
11	19*	13
12	19*	4
13	19*	12
14	34*	0
15	22*	1
16	22*	6

9,3,L

0	75	81
1	102	103
2	55	68
3	26*	14
4	53	55
5	15*	15
6	30*	35
7	58	60
8	49*	33
9	17*	28
10	17*	6
11	19*	34
12	19*	2
13	19*	4
14	22*	1
15	22*	14
16	22*	12

9,4,L

0	30*	12
1	107	118
2	85	114
3	43*	38
4	26*	8
5	15*	3
6	134	144
7	64	64
8	47*	29
9	26*	15
10	17*	2
11	19*	20
12	19*	5
13	19*	6
14	19*	7
15	22*	13

9,5,L

0	90	84
1	292	316
2	264	266
3	241	258
4	124	138
5	55	49
6	30*	14
7	30*	27
8	17*	19
9	41*	47
10	45*	47
11	41*	15
12	19*	2
13	19*	18
14	22*	11
15	22*	1

9,6,L

0	51	62
1	87	82
2	130	124
3	43*	57
4	15*	27
5	15*	24
6	58	46
7	17*	9
8	75	82
9	81	78
10	19*	18
11	19*	11
12	43*	19
13	51*	26
14	19*	6
15	22*	12

9,7,L

0	43*	26

9,7,L

1	15*	16
2	28*	23
3	15*	14
4	15*	11
5	34*	13
6	36*	30
7	30*	16
8	96	76
9	19*	33
10	19*	2
11	19*	4
12	22*	3
13	22*	3
14	32*	16

9,8,L

0	17*	16
1	58	49
2	17*	26
3	17*	9
4	17*	25
5	28*	22
6	17*	18
7	19*	29
8	19*	21
9	19*	32
10	56*	16
11	19*	14
12	22*	6
13	32*	6

9,9,L

0	17*	16
1	17*	2
2	17*	9
3	17*	20
4	79	88
5	19*	15
6	41*	4
7	30*	1
8	19*	14
9	19*	7
10	19*	1
11	22*	1
12	22*	7
13	22*	5

9,10,L

0	17*	11
1	19*	29
2	19*	18
3	56*	33
4	17*	8
5	19*	5
6	51*	18
7	19*	15
8	64*	37
9	30*	20
10	39*	7
11	22*	2
12	22*	4

10,0,L

0	19*	23
2	34*	24
4	85	88
6	115	122
8	17*	26
10	43*	38
12	19*	6
14	19*	7
16	51*	33

10,1,L

0	55	59
1	188	191
2	13*	16
3	171	191
4	271	287
5	47*	43
6	188	197
7	87	81
8	34*	23
9	26*	15
10	36*	25
11	66	56
12	19*	13
13	19*	10
14	22*	7
15	22*	17
16	49*	14

10,2,L

0	66	73
1	51	49
2	64	68
3	53	45
4	45*	42
5	58	44
6	15*	22
7	68	71
8	64	48
9	17*	32
10	17*	12
11	96	74
12	36*	21
13	19*	5
14	32*	11
15	19*	7
16	22*	12

10,3,L

0	124	129
1	13*	19
2	15*	20
3	49*	60
4	107	90
5	87	82
6	130	139
7	17*	6
8	39*	8
9	17*	3
10	32*	17
11	19*	6
12	19*	5
13	19*	2
14	19*	9
15	43*	4

10,4,L

0	151	151
1	407	423
2	160	172
3	85	88
4	43*	40
5	15*	13
6	49*	54
7	17*	12
8	17*	7
9	17*	24
10	17*	3
11	32*	4
12	28*	14
13	19*	6
14	19*	12
15	22*	13

10,5,L

0	53	52
1	333	334
2	145	147
3	34*	8
4	190	196
5	15*	6
6	49*	15
7	34*	16
8	43*	36
9	39*	25
10	75	69
11	41*	18
12	19*	16
13	19*	6
14	22*	9
15	22*	5

10,6,L

0	15*	25
1	34*	18
2	100	93
3	58	67
4	100	105
5	36*	37
6	17*	18
7	17*	14
8	75	69
9	126	113
10	19*	15
11	47*	24
12	19*	5
13	22*	11
14	56*	9

10,7,L

0	53	56
1	49*	47
2	154	155
3	17*	6
4	17*	11
5	17*	14
6	39*	11
7	34*	7
8	100	83
9	60*	64
10	34*	5
11	34*	31
12	19*	3
13	22*	20
14	22*	19

10,8,L

0	15*	8
1	34*	20
2	17*	25
3	66	58
4	17*	6
5	17*	8
6	19*	10
7	19*	33
8	49*	23
9	47*	15
10	19*	3
11	19*	18
12	41*	4
13	30*	17

10,9,L

0	17*	14
1	60	63
2	36*	42
3	17*	15
4	17*	7
5	41*	25
6	34*	3
7	49*	25
8	36*	2
9	19*	18
10	58*	6
11	22*	10
12	41*	9

10,10,L

0	17*	4
1	19*	43
2	19*	35
3	19*	31
4	19*	12
5	34*	2
6	39*	9
7	19*	19
8	54*	3
9	19*	2
10	22*	5
11	22*	3

VITA 2

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